Developments in signal processing for computerised diagnosis in clinical neurophysiology

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DEVELOPMENTS IN SIGNAL PROCESSING FOR COMPUTERISED DIAGNOSIS IN CLINICAL NEUROPHYSIOLOGY

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Abstract

The aim of this study was to apply signal processing techniques to a potential known as the contingent negative variation (CNV) in order to aid detection of schizophrenia, Parkinson's disease (PD) and Huntington's Disease (HD). A data recording system was constructed and used to obtain data from 20 schizophrenic patients, 16 PD patients, 21 "at-risk" of HD patients, 11 HD patients and 43 normal control subjects. The data included the CNV, electro-oculograms (required for the preprocessing of the CNV) and the subjects reaction times to an acoustic stimulus. The CNV waveforms were initially preprocessed. This reduced the effects of background electroencephalogram and ocular artefact potentials.

The CNV waveforms were then processed using a method which involved the discrete Fourier transform (DFT) and discriminant analysis. This method developed from the work of Martin Nichols and Michael Coelho. It was possible to successfully identify the majority of the patients using this method. In order to reduce the complexity of patients' identification a different method of CNV signal processing was considered. This involved obtaining the CNV features in the time domain and using them in neural networks. This method was as effective as the method which used DFT and discriminant analysis in identifying the patients. To establish whether HD could presymptomatically be detected in the at-risk of HD group, the CNV was analysed using principal component analysis (PCA) and Ward's clustering method. This resulted in identification of 7 patients who were suggested would develop HD. The subjects' reaction times were also analysed. This indicated that the reaction times of schizophrenic, PD, HD and some at-risk of HD patients were significantly different from the reaction times of their normal control subjects.

Declaration

I hereby declare that whilst registered as a candidate for the degree of the Doctor of Philosophy with the Council for National Academic Awards I have not been registered for any other qualification of the CNAA or any other examination body.

Signed

M.R. Saatchi

Courses Attended

Lectures in Signal Processing (Intended for Final Year B.Sc. Hons. Students), October 1988 - February 1989.

Lectures in Multivariate Methods (Intended for Polytechnic Graduate Diploma/M.Sc. Students), October 1988 - March 1989.

The List of Publications

Saatchi, R. and Jervis, B.W., (1989), "A PC-based instrument for recording CNVs", Proceedings of the EEG Society Scientific Meeting, Aston University, Birmingham.

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Jervis, B.W., Saatchi, M.R., Allen, E., Hudson, N. and Oke, S., (1991), "An investigation of presymptomatic diagnosis of Huntington's disease using the contingent negative variation", Proceedings of the British Society for Clinical Neurophysiology Annual General Meeting", The Royal London Hospital, London.

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Conferences Attended

IEE colloquium on "The application of artificial intelligence techniques to signal processing", IEE Savoy Place, London, 1989.

The Electrophysiological Technologists' Association Meeting, (also gave a talk in this meeting, title: "Analysis of the CNV waveform for diagnosis of schizophrenia, Huntington's disease and Parkinson's disease", Royal Devon and Exeter Hospital, 1990.

Contents

Glossary

A/D	Analogue to Digital Convertor
AEP	Auditory Evoked Potential
AR	At-Risk
CNV	Contingent Negative Variation
CT	Computed Tomography
DA	Discriminant Analysis
DF	Degrees of Freedom
DFT	Discrete Fourier Transform
DOS	Disk Operating System
DSM	Diagnostic and Statistical Manual of Mental Disorders
ECG	Electrocardiogram
EEG	Electroencephalogram
EOG	Electro-oculogram
EP	Evoked Potential
ERP	Event-Related Potential
FFT	Fast Fourier Transform
FIR	Finite Impulse Response
HEX	Hexadecimal
HC	Huntington's Chorea
HD	Huntington's Disease
IIR	Infinite Impulse Response
ISI	Inter-Stimulus Interval
ISR	Interrupt Service Routine
ITI	Inter-Trial Interval
LED	Light Emitting Diode
MRI	Magnetic Resonance Imaging
OA	Ocular Artefact

P	Probability
PC	Personal Computer
PCA	Principal Component Analysis
PD	Parkinson's Disease
PET	Positron Emission Tomography
PGA	Programmable Gain Amplifier
PGR	Psychogalvanic Response
PINV	Post-Imperative Negative Variation
PPI	Programmable Peripheral Interface
RAM	Random Access Memory
SAS	Statistical Analysis Systems
SDA	Stepwise Discriminant Analysis
SEP	Somatosensory Evoked Potentials
S/H	Sample and Hold
STD	Standard Deviation
VCVS	Voltage-Controlled Voltage Source
VEP	Visual Evoked Potential
WD	Window Detector

List of Diagrams

Chapter 1 Summary

An instrumentation system was constructed and was used to record the data from 20 schizophrenic, 16 Parkinson's disease (PD), 11 Huntington's disease, 21 "at-risk" (AR) of HD patients and 43 normal control subjects. In order to improve the signal (ie. the contingent negative variation, CNV) to noise (ie. the background EEG activity and ocular artefact) ratio, the CNV waveforms were preprocessed using a method developed by Nichols [1982] and Coelho [1988]. The preprocessed CNV responses were then analysed by: i) using the Fourier transform and discriminant analysis, ii) using the CNV time domain features in neural networks and iii) applying principal component analysis and cluster analysis. The reaction times of the subjects to an acoustic stimulus were also analysed.

1.1 Identification of Schizophrenic, Parkinson's Disease and Huntington's Disease Patients by Frequency Analysis and Discriminant Analysis of the CNV

This method involved applying the discrete Fourier transform (DFT) to pre- and post-stimulus sections of the CNV waveforms and then applying four statistical tests to the resulting harmonic frequency components of the pre- and post-stimulus spectra. The four statistical tests were originally designed by Nichols [1982] to detect phase and amplitude changes in CNV spectra. This process produced a set of variables. A variable subset which best identified the patients was selected and then used in a discriminant analysis program. A leave-one-out method was used to ensure the data included during the calibration phase of the discriminant analysis program were not used during the test phase. The method successfully identified the majority of schizophrenic, PD and HD patients from normal subjects and it was useful in distinguishing between the patients from the above three categories. The performance of the discriminant analysis was best when distinguishing between the HD patients and normal subjects (ie. 100%). This indicated that perhaps the

effects of HD on the CNV is more severe than the effects of schizophrenia and PD on the CNV. The success rates obtained when distinguishing the patients from their normal control subjects were higher than the success rates obtained when distinguishing between the patients from different categories. This might be because some of the CNV abnormalities in schizophrenia, PD and HD overlap.

1.2 Identification of Schizophrenic, Parkinson's Disease and Huntington's Disease Patients by Using the CNV Time Domain Features in Neural Networks

Neural networks were applied to the CNV waveforms of the schizophrenic, PD and HD patients and their normal control subjects. The CNV features (variables) used were obtained by averaging every four consecutive sample values from a CNV section 512ms prior to the imperative-stimulus. This generated 16 CNV features. As the time taken for the CNV to return to its baseline has been shown to be important in identifying patients with disorders such as schizophrenia, PD and HD (see chapter 2) a seventeenth feature which reflected this effect was also included. The patients from each category and their normal control subjects were divided into two groups. The CNV responses from the first group were used for training the neural networks and the CNV responses from the second group were used to test the effectiveness of the neural networks. The effect of changing the number of nodes in the hidden layer(s) of the neural networks was investigated. The neural networks successfully identified the schizophrenic, PD, and HD patients from normal subjects. They performed best when distinguishing between the HD patients and normal subjects (ie. 100% success rate). This was in line with the results obtained from the other two methods of patients' differentiation.

1.3 Presymptomatic Detection of Huntington's Disease and Identification of Schizophrenic, Parkinson's Disease and Huntington's Disease Patients by Applying Principal Component Analysis and Cluster Analysis to the CNV

The presymptomatic identification of HD patients is valuable as it can help the individuals AR of HD decide whether they should have children. Discriminant analysis was not suitable for presymptomatic identification of HD patients as it was based on a supervised learning method. The clustering method is an unsupervised learning method and therefore was used for this purpose. The procedure for CNV feature extraction was the same as that used for the neural network method. The CNV features were transformed using principal component analysis.

Initially principal component analysis and clustering were used to distinguish between schizophrenic, PD and HD patients and normal subjects. Application of principal component analysis and cluster analysis resulted in the identification of the majority of schizophrenic, HD and PD patients. In line with the other two methods of patients' differentiation this method was most effective in identifying the HD patients.

The principal component analysis and cluster analysis were then applied to CNV responses of 21 AR of HD patients and their normal control subjects. Seven AR of HD patients were identified as "abnormal" and it was suggested that they would develop HD. The remaining 14 AR of HD patients were identified as "normal" AR of HD patients.

A Two-tailed t-test was used to examine the CNV amplitudes in the abnormal AR of HD patients, normal AR of HD patients and their normal control subjects. The CNV amplitudes of abnormal AR of HD patients and their normal control subjects were significantly different ($p<0.001$, $df=12$). The CNV amplitudes of normal

AR of HD patients were not significantly different from those of their normal control subjects.

The CNV amplitude analysis of the AR of HD patients also indicated that the changes in the CNV responses of HD patients appeared prior to the onset of HD. This finding is in agreement with the studies of Josiassen et al. [1982], Oepen et al. [1982], Josiassen et al. [1984], Noth et al. [1984], Hennerici et al. [1985] and Hömberg et al. [1986] when other event-related potentials (ERPs) were analysed in AR of HD patients (refer to chapter 2 for detail).

1.4 Reaction Times Analysis of Schizophrenic, Parkinson's Disease, Huntington's Disease and At-Risk of Huntington's Disease Patients

During the data recordings, 32 reaction times were recorded for each subject. The reaction times were averaged and used in a two-tailed t-test. It was found that the reaction times of schizophrenic, PD and HD patients were significantly different from the reaction times of their normal control subjects ($p < 0.001$).

The reaction times of the AR of HD patients were not significantly different from the reaction times of their normal subjects. A similar result was obtained when the reaction times of the AR of HD patients who were identified as "normal" in chapter 9 were compared with their normal control subjects. But when the reaction times of the "abnormal" AR of HD patients were compared with the reaction times of their normal control subjects, they were significantly different ($p < 0.05$, $df = 12$).

In several studies it has been shown that the reaction time tends to be shorter following a large CNV and longer following a low amplitude CNV [Tecce, 1972]. As the mean CNV amplitude of the abnormal AR of HD patient group was about

1/3 of that in the normal control group, this prolongation of the reaction times in the abnormal AR of HD patients was in agreement with findings related to the relationship between the CNV amplitude and the reaction time.

1.5 Overall Remarks

In this study three different methods were successfully used to differentiate schizophrenic, PD and HD patients. The results indicated that all three methods were valuable in identifying these patients. The patient differentiation method which involved the use of the discrete Fourier transform and discriminant analysis was the most complex method. Neural networks were used in order to find an effective but less complicated method of identifying the patients. The application of principal component analysis and clustering resulted in the identification of 7 abnormal AR OF HD patients. The reaction times in the subjects were also analysed and it was found that the reaction times of schizophrenic, PD, HD and abnormal AR of HD were significantly different from the reaction times of their normal control subjects.

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Chapter 2 Introduction

This project was a continuation of previous studies [Nichols, 1982] [Coelho, 1988]. Nichols [1982] recorded the contingent negative variation (CNV) waveforms of 8 Huntington's Disease (HD) patients and 6 normal subjects and devised a CNV preprocessing procedure. The preprocessing is necessary in order to retrieve the CNV from background noise sources (the CNV preprocessing is described in chapter 6). He then investigated the composition of the CNV by using signal processing and statistical methods. Coelho [1988] enhanced the Nichols' CNV preprocessing method. He also applied signal processing and statistical techniques to the data recorded by Nichols [1982] in order to differentiate between HD patients and normal subjects (see chapter 7 for detail). The main problem with the patients' identification method used by Coelho [1988] was that it required very complicated and time consuming analysis of the CNV.

For this project the aim was to construct a data recording system and use it to record the CNV waveforms of HD, "at-risk" (AR) of HD, Parkinson's Disease (PD), schizophrenic patients, and their age and sex matched normal control subjects. Then preprocess the CNV waveforms. It was intended to initially use the patient identification method employed by Coelho [1988] and differentiate between HD, PD, schizophrenic and normal subjects. Then develop another less complicated method of identifying the patients. Presymptomatic detection of HD patients is important as it could be used as a mean of reducing the number of individuals with that disorder. Therefore, it was planned to investigate whether HD could be presymptomatically diagnosed using the CNV.

The reason for using the CNV to identify HD, PD and schizophrenic patients is that although these disorders could be related to some specific symptoms and pathological changes, it can sometimes be difficult for a neurophysiologist or psychiatrist to distinguish between them. This is because some of the symptoms

and pathological changes observed in the patients with these disorders can be similar.

In this chapter the symptoms and the brain structural changes observed in schizophrenic, PD and HD patients are discussed. A description of the electroencephalogram (EEG), event-related potentials (ERPs) and the CNV is provided, and the relevant studies in ERPs in schizophrenia, PD, HD and AR of HD are reviewed.

2.1 Description of the Disorders Included in this Study

2.1.1 Schizophrenia

The symptoms associated with schizophrenia can be grouped into "type 1" and "type 2" [Crow and Johnstone, 1987]. Type 1 includes psychotic symptoms which are generally referred to as "positive" because they cause abnormality by their presence eg. hallucinations and delusions. Type 2 includes symptoms which are generally referred to as "negative" because a normal function is missing. Symptoms such as poverty of speech, lack of self-care and anergia are considered as negative symptoms. The symptoms observed in a schizophrenic patient could be mainly positive, negative, or they can be a mixture. The positive and negative symptoms can be observed at different times in the course of the illness, or sometimes concurrently. Untreated schizophrenia tends to be progressive (with some exceptions) and may reach a state of irreversible defect [Miller, 1989].

There are some indications of a general increase in cerebral activity in some stages of schizophrenia. For example, an increased power in certain frequency bands of the brain's electrical activity has been observed in early stages of schizophrenia [Mukunda, 1986]. There are two possible causes for this excess neural activity. It may be due to excess connectivity in the forebrain, or in crucial parts of it

[Nasrallah et al., 1986], or it may be as a result of neurochemical imbalances with respect to the neurotransmitters which control signal gain in the forebrain [Wong et al., 1987]. Ben-Ari [1985] reported that the endogenous release of excitory transmitters led to the brain cell destruction, therefore suggesting that if the activity of neurons becomes too excessive, it might lead to their destruction.

Several structural brain abnormalities have been observed in schizophrenic patients [Ron and Harvey, 1990]. The commonest were enlargement of the lateral and third ventricles (see Figures (2.1) and (2.2)) and cortical atrophy [Revely, 1985] [Weinberger et al., 1983]. There is also evidence for a reduction in volume of the hippocampus (see Figure (2.3)) in schizophrenic patients [Falkai and Bogerts, 1986]. Young et al. [1991] using magnetic resonance imaging (MRI) found that the parahippocampal gyrus (see Figure (2.3)) was smaller on the left side in 31 schizophrenic patients but not in 33 age and sex matched normal control subjects. They reported that in schizophrenic patients, ventricular enlargement and cerebral atrophy were significantly related to severity of the symptoms. Some investigators found a distinct relationship between the structural brain abnormalities and positive and negative symptoms in patients with schizophrenia. Marks and Luchins [1990] provided a review of some of these reports.

The identification of patients with schizophrenia has been based on monitoring the symptoms and observation of the structural brain abnormalities related to the disorder.

2.1.2 Parkinson's Disease

PD was originally described by James Parkinson [1817]. PD is a progressive neurologic disorder. Its main clinical symptoms are: i) body tremors at rest. The tremors mainly affect a limb or limbs but they may also be observed in other areas such as jaw and lips, ii) muscle rigidity. This may cause stiffness and muscle

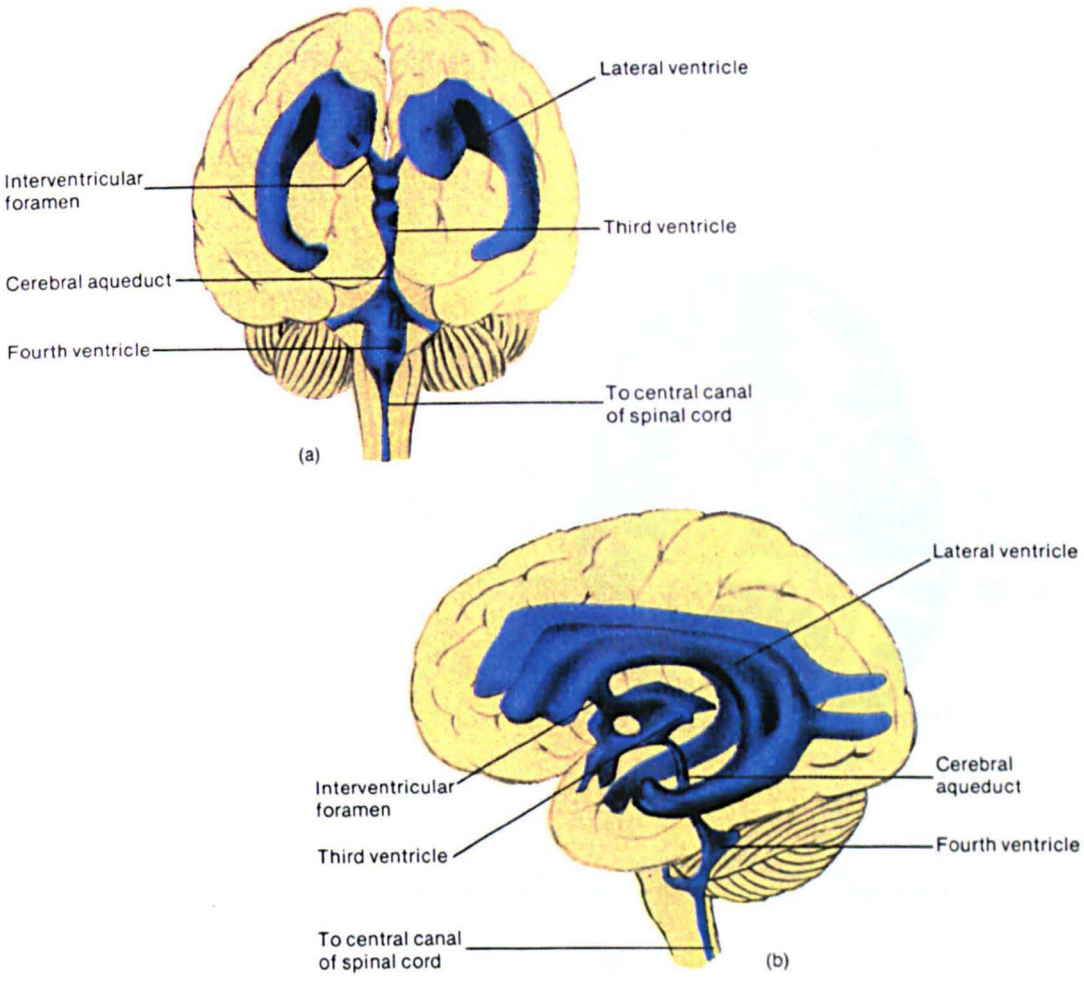

Figure 2.1 The ventricles of the brain. (a) An anterior view, (b) a lateral view (this Figure was obtained from Fox [1990]).

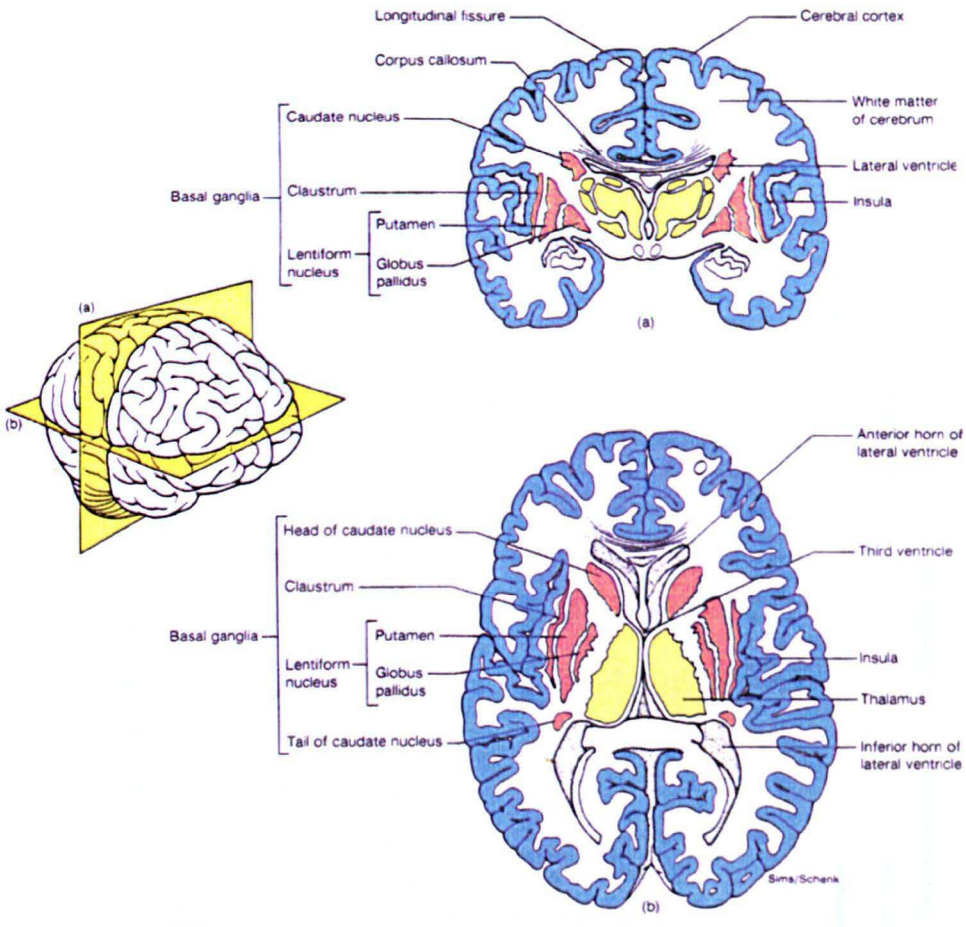

Figure 2.2 Sections through the cerebrum and diencephalon. (a) A coronal section, (b) a transverse section (this Figure was obtained from Fox [1990]).

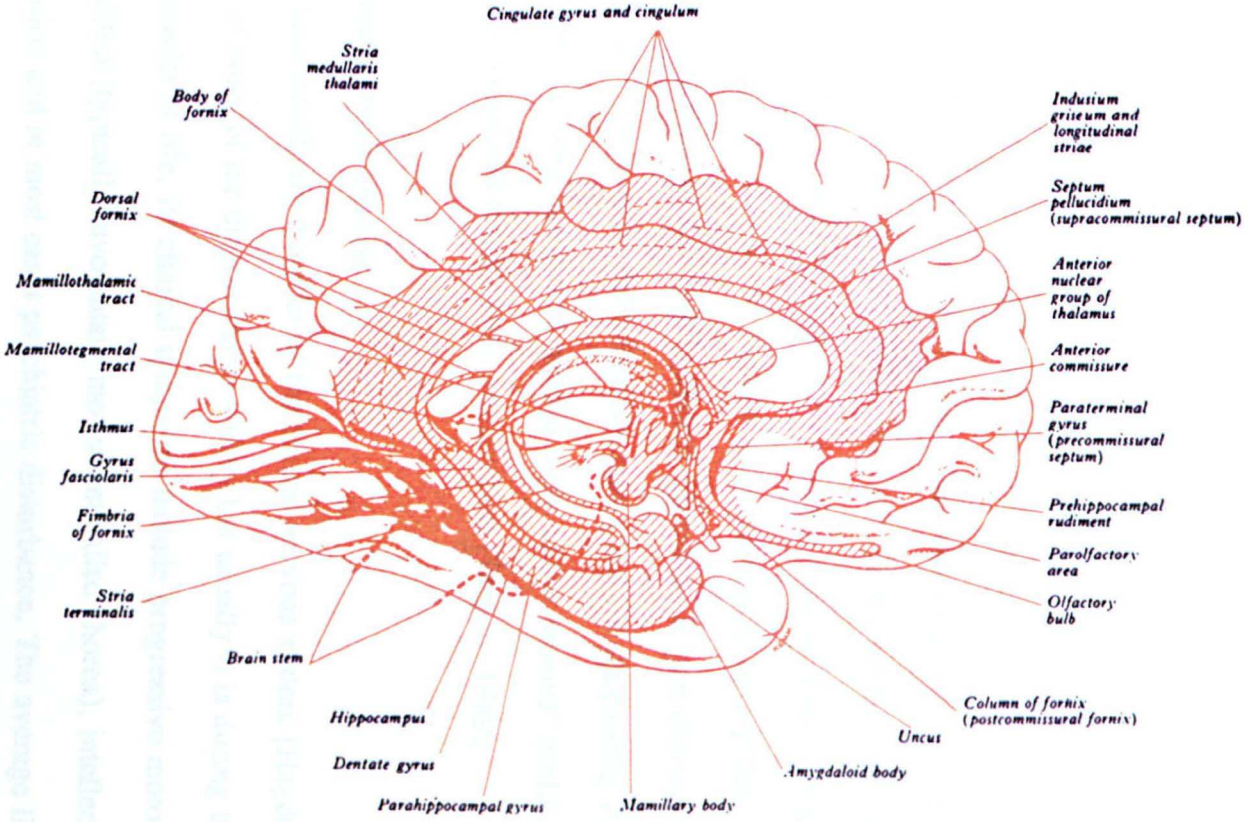

Figure 2.3 The locations of the hippocampus and parahippocampal gyrus in the brain (this figure was obtained from Guyton [1977]).

discomfort, iii) slowness of active movements (such as rising from a chair) and iv) postural instability. This can cause patients to fall. A number of secondary clinical symptoms such as dementia and depression may also be observed in some PD patients.

The cause of PD is unknown. The studies in progress to identify its cause include a search for an environmental toxin [Stern and Hurtig, 1988]. PD is characterised pathologically by: i) degeneration of the dopaminergic neurons from the substantia nigra [Bennett, 1988]. The substantia nigra (see Figure (2.4)) is a small nucleus considered a part of the basal ganglia. The anatomy of the basal ganglia is complex and their details poorly known. The basal ganglia are composed of neuron cell bodies located deep within the white matter of the cerebrum and they form part the neural pathway that controls motor function [McKenzie et al., 1984] and ii) the appearance of Lewy bodies in the substantia nigra [Gibb, 1987]. Lewy bodies consist of structurally altered filaments, in part derived from neurofilament. There is no definitive laboratory test for diagnosing PD, therefore, its diagnosis has been based on a careful study of the patients' medical history and thorough physical and neurological examination [Vernon, 1989].

2.1.3 Huntington's Disease

HD is a fatal hereditary disorder of the central nervous system [Hayden, 1981]. The age of onset of the disease varies widely but usually it is during the third and fourth decades of life. Its clinical symptoms include progressive motor abnormalities (typically involuntary movement called chorea), intellectual deterioration and in most cases psychiatric disturbance. The average life span after the onset of the disease is between 15 and 20 years. The disease is inherited through a defective gene localised to the short arm of chromosome 4 [Gusella et al., 1983]. An offspring of an affected parent can have a 50% chance of receiving the defective gene. Studies using computed tomography (CT) and positron

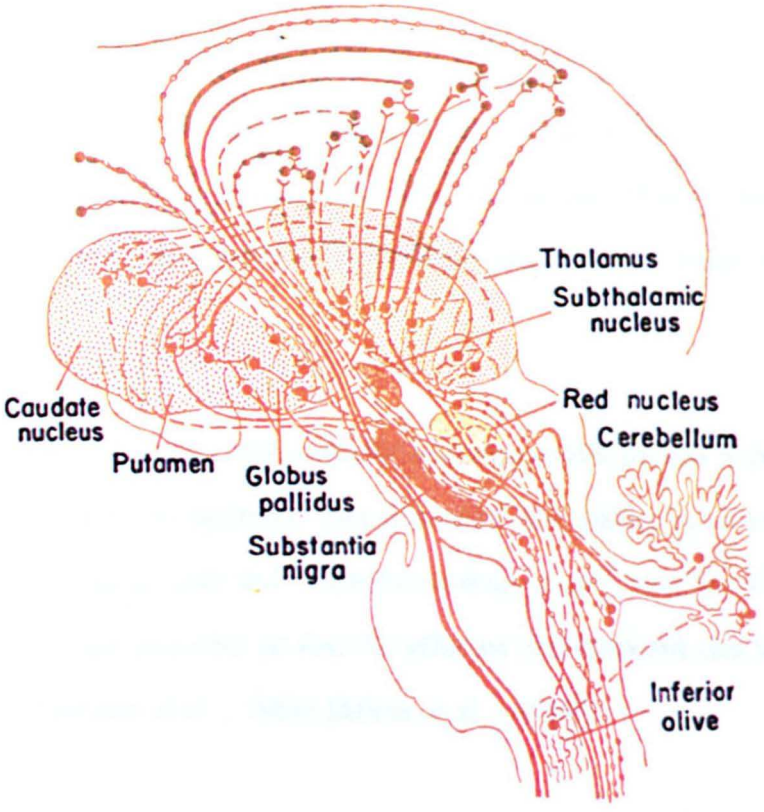

Figure 2.4 The location of the substantia nigra in the brain (this Figure was obtained from Guyton [1977]).

emission tomography (PET) show neuropathological changes in several parts of the brains of HD patients. The affected areas include the globus pallidus (see Figure (2.5)) and frontal cortex [Hayden, 1981] [Adams et al., 1984], but the brunt of the changes (typically severe neuronal loss) are in the striatum [Mazziotta, 1989]. The striatum (see Figure (2.5)) is part of the basal ganglia and is referred to two masses of nuclei called the caudate nucleus and putamen. Several nerve pathways pass from the cerebral cortex (particularly the so-called "pre-motor areas") to the striatum.

As there is no definitive test for diagnosing HD, therefore, its diagnosis has been based on a positive family history (ie. if the patients have affected parents), indications of progressive motor disability and psychiatric disturbance, and observation of relevant structural abnormalities of the brain using PET and CT scans.

A genetic presymptomatic test for individuals AR of HD is possible but it excludes some AR of HD patients. This is because the marker used in the test does not detect the gene itself and therefore testing is only possible if suitable family members are available so that the affected chromosome can be identified [Jackson, 1987] [Harper et al., 1988] [Mirsa et al., 1988].

2.2 Description of Electroencephalogram and Event-Related Potentials

The electroencephalogram (EEG) is the name given to electrical activity of the brain. The first reported observation of EEG was made by a British physiologist called Richard Caton. He studied the brains of rabbits and monkeys and reported: "the external surface of the (brain's) grey matter is usually positive in relation to the surface of the section through it. Feeble currents of varying direction pass through the multiplier when the electrodes are placed on two points on the external surface (of the brain), or one electrode on the grey matter, and one on the surface

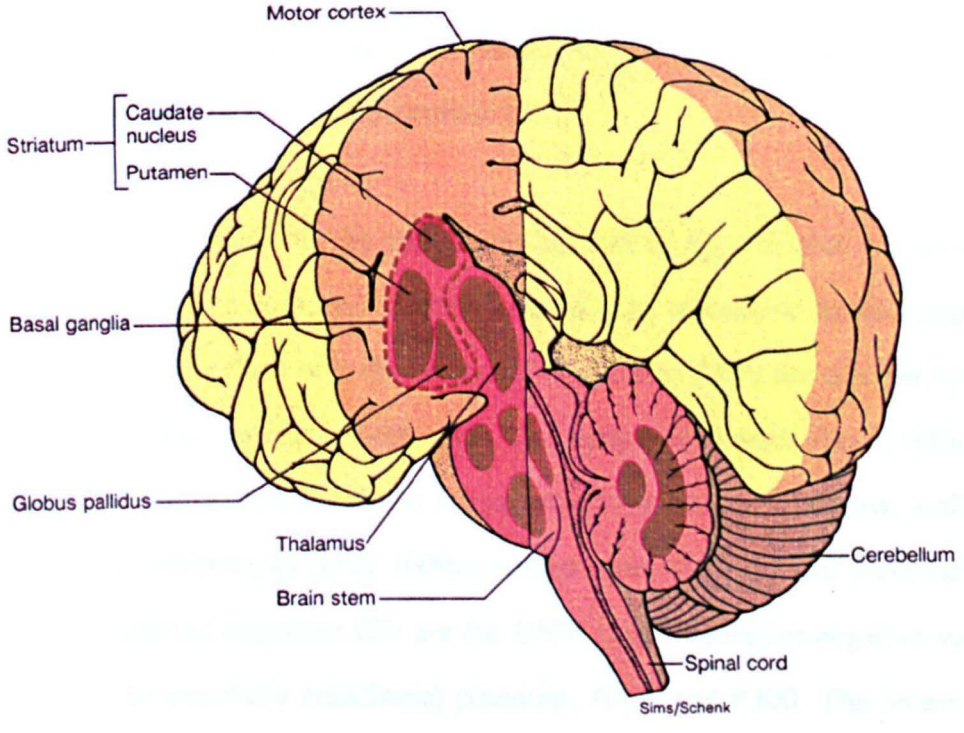

Figure 2.5 The locations of the globus pallidus and striatum in the brain (this figure was obtained from Fox [1990]).

of the skull" [Caton, 1875]. Berger's [1929] discovery that EEG could be recorded from the intact scalp led to the development of modern electroencephalography in man. The EEG provides information about underlying or ongoing brain functioning.

ERPs are potential changes in EEG that occur in association with an eliciting event. In some articles the term evoked potential (EP) is used instead of ERP. In this thesis both terms are used and they are considered synonymous. There are several types of ERPs (Cooper et al. [1980] have provided a review of ERPs). They include auditory evoked potentials (AEPs), visual evoked potential (VEPs) and somatosensory evoked potentials (SEPs).

SEPs are usually elicited by stimulating the left or right median nerves at the wrist with brief (0.1ms duration) electrical pulses. The stimulator for eliciting VEPs may be a strobe flash or a checkerboard flash. The AEPs are elicited by clicks or tones presented to one or both ears. The early components (up to 100ms) of the ERPs are determined mainly by the nature of the evoking stimulus, while the following components (after 100ms) reflect more the cognitive processes. The widely reported cognitive EPs are the CNV, post-imperative negative variation (PINV), Bereitschafts (readiness) potential, N100 and P300. The letters "N" and "P" describe the polarities of the waves, ie. "P" represents a positive wave and "N" represents a negative wave. The number following the polarity letter indicates the wave's approximate peak latency. For example, N100 is a negative wave that reaches its maximum amplitude at about 100ms after the onset of the evoking stimulus.

The amplitude of N100 is dependent on factors such as expectedness of the stimulus and the attention paid to it. The P300 is a positive wave that reaches its peak between 300 and 500ms after the onset of the eliciting stimulus. To evoke the

P300 in AEPs, the patient is requested to detect an infrequently occurring tone burst from a background sequence of another tone which has a different pitch. The P300 may reflect the ability of the individuals to process information [Baribeau-Braun et al., 1983]. The Bereitschafts potential is generated as a result of a voluntary motor response and it may reflect preparatory activity in the supplementary motor area of the cortex [Dick et al., 1989]. The CNV is described in detail in the next section. The PINV is closely related to the CNV and is also described in the next section.

2.2.1 Description of the Contingent Negative Variation

The CNV was first described by Walter et al. [1964]. Since then it has been described in a number of articles. Recently McCallum [1988] and Tecce and Cattanach [1987] have provided a review of the nature of the CNV. The CNV is a negative shift in EEG as compared to the potential of the electrical reference electrode. Commonly electrodes placed on linked earlobes are used as the reference. The elicitation of the CNV involves presentation of a warning stimulus, S1 (eg. a click) to warn the subject of the upcoming imperative stimulus, S2 (this can be a tone). The subject is requested to respond to the imperative stimulus by performing a motor function, eg. by pressing a push-button to terminate the tone.

The CNV is susceptible to contaminations, mainly by ocular artefact potentials. The causes of the ocular artefact potentials are eye movements and blinks and they are described in chapter (6). The CNV is also usually obscured by the background EEG. The CNV therefore, has to be preprocessed prior to analysis. The preprocessing method used was developed by Nichols [1982] and Coelho [1988] and it is described in chapter (6).

A schematic drawing of a preprocessed averaged CNV is shown in Figure (2.6). Figures (2.7)-(2.11) show the CNV response in a normal subject, a schizophrenic patient, a PD patient, an HD patient and an AR of HD patient respectively. Figures (2.12)-(2.16) show the preprocessed averaged (over 8 trials) CNV responses in the above subjects. The negative shift follows the onset of the warning stimulus and it normally returns to its original baseline rapidly after the subject response to the imperative stimulus. In some cases the CNV takes an abnormally longer time to return to its original baseline. The negative potential which appears as a continuation of the CNV following the imperative stimulus is known as the post-imperative negative variation (PINV). Figure (2.17) shows the PINV in a PD patient.

The CNV was reported to have an early and a late component [Rohrbaugh et al., 1976] [Rohrbaugh and Gaillard, 1983]. The early component develops in response to the warning stimulus, its magnitude is maximum over the frontal cortex, and it is dependent on the characteristics of the warning stimulus (eg. duration and modality) [Rohrbaugh and Gaillard, 1983]. The late component is believed to be related to preparation for motor response and it has a more central distribution over areas of the cortex Rohrbaugh et al. [1976]. The physiology of the CNV is complex and is not completely understood. The CNV has been suggested to originate from the frontal and central areas of the cortex. Some sub-cortical areas of the brain such as the caudate nucleus of the thalamus were also believed to have a role in its production [Tecce, 1972] [Cohen, 1974].

The CNV was used for the identification of patients with schizophrenia, PD and HD because: i) the main source of the CNV (ie. the frontal cortex) is an affected area in schizophrenia, PD and HD [Goldman-Rakic, 1987], ii) several studies have indicated that the CNV was altered in patients with any of these disorders (see section 2.3 for detail) and iii) the CNV is considered to be a measure of the

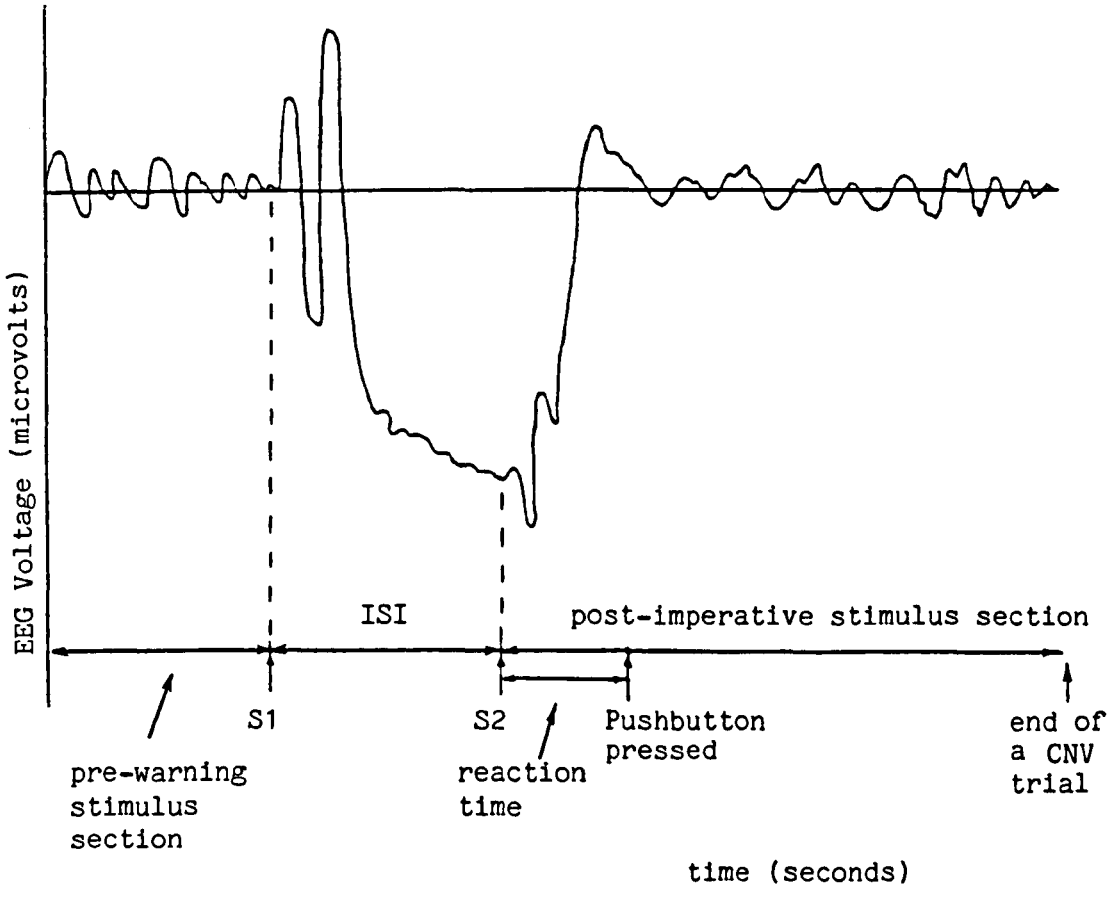

Figure 2.6 A Schematic drawing of a preprocessed averaged CNV waveform.

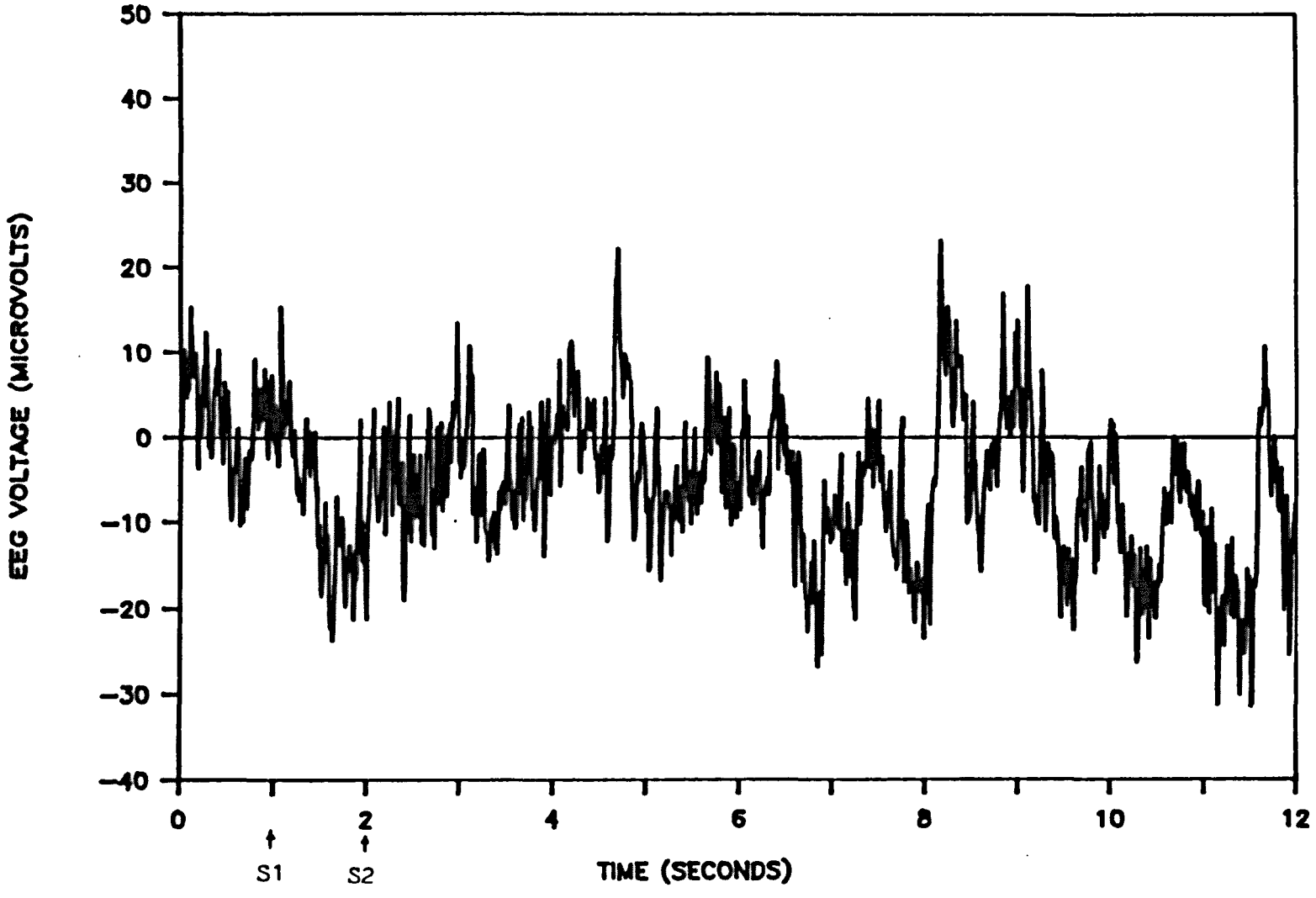

Figure 2.7 The CNV response in a normal subject.

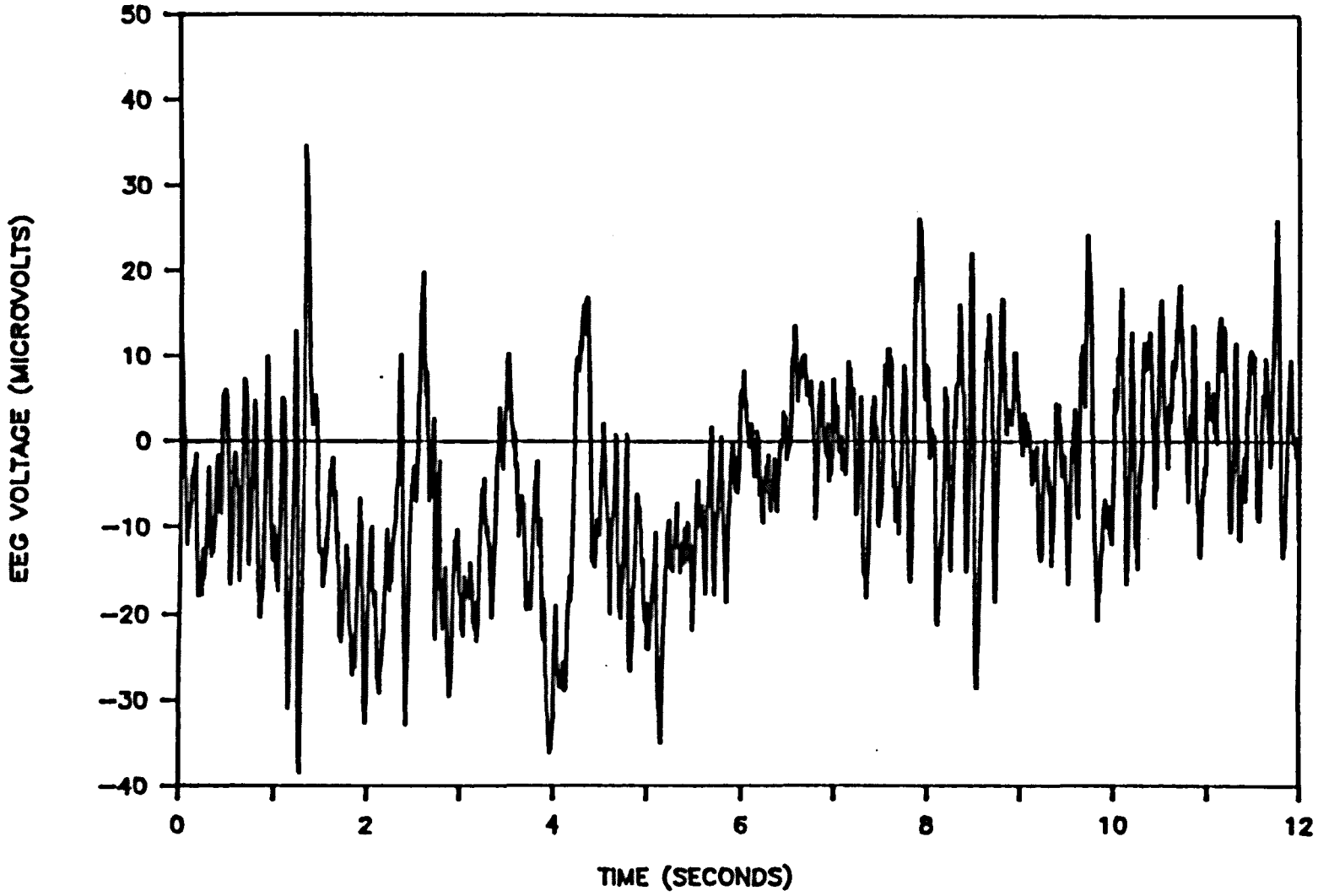

Figure 2.8 The CNV response in a schizophrenic patient.

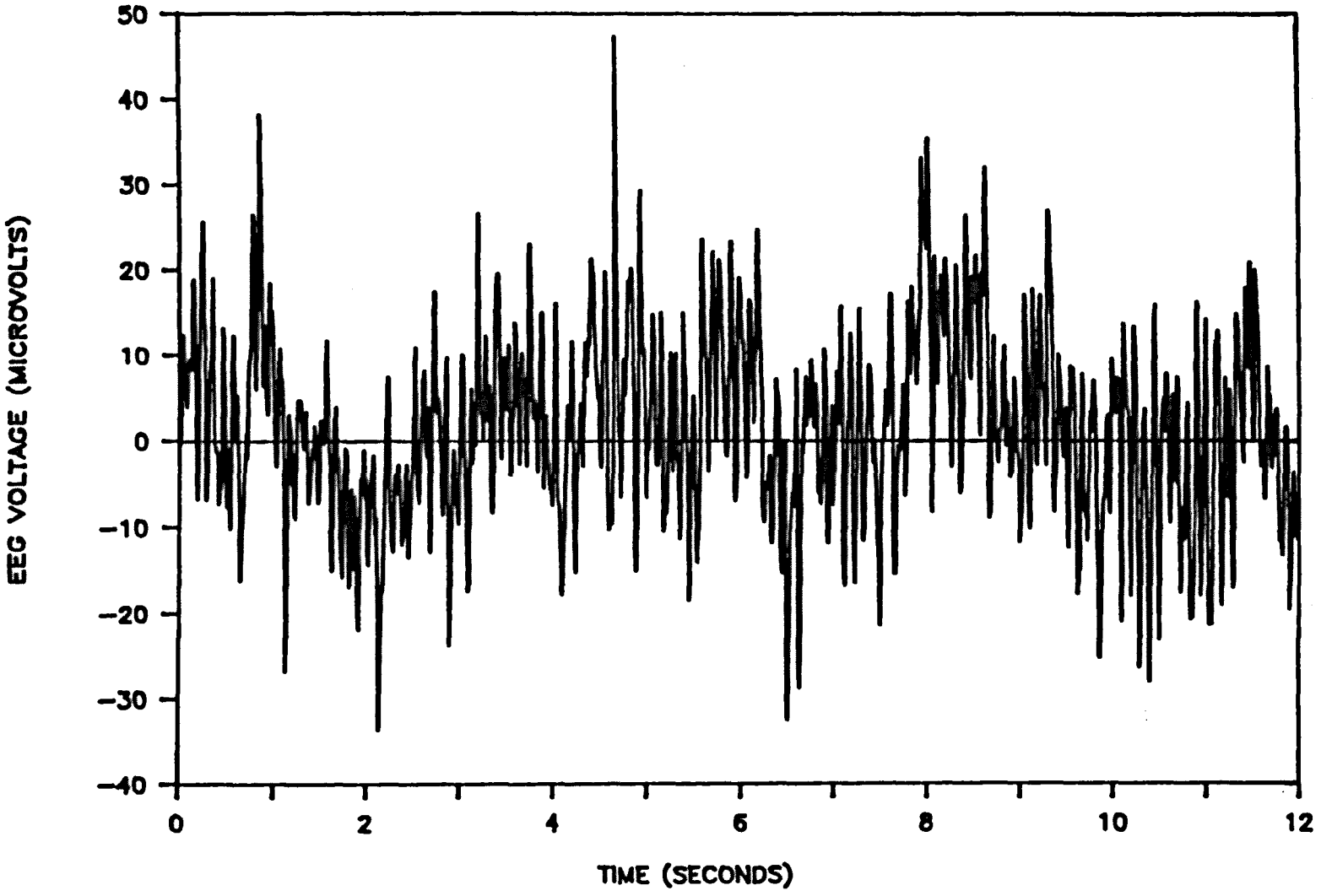

Figure 2.9 The CNV response in a Parkinson's disease patient.

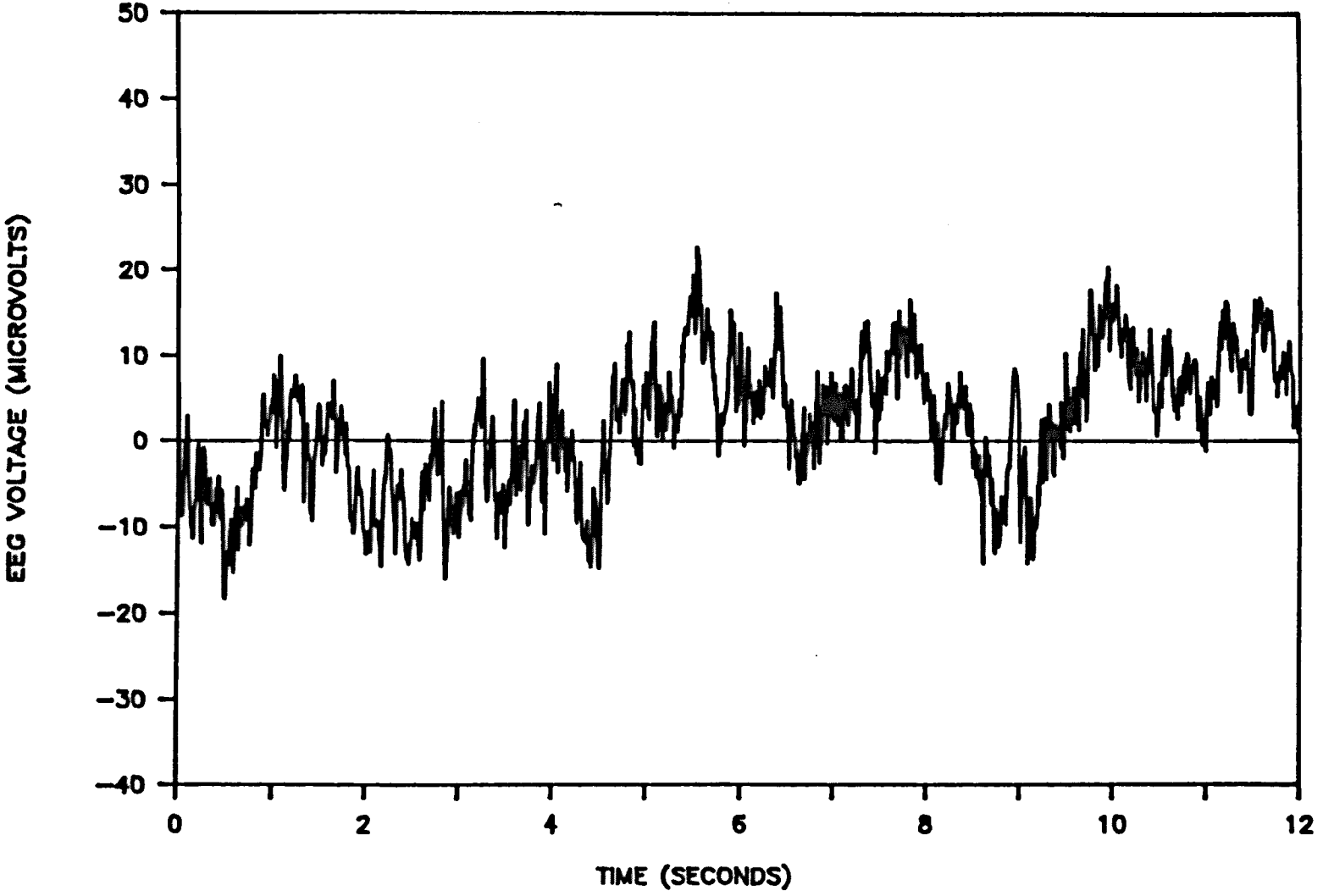

Figure 2.10 The CNV response in a Huntington's disease patient.

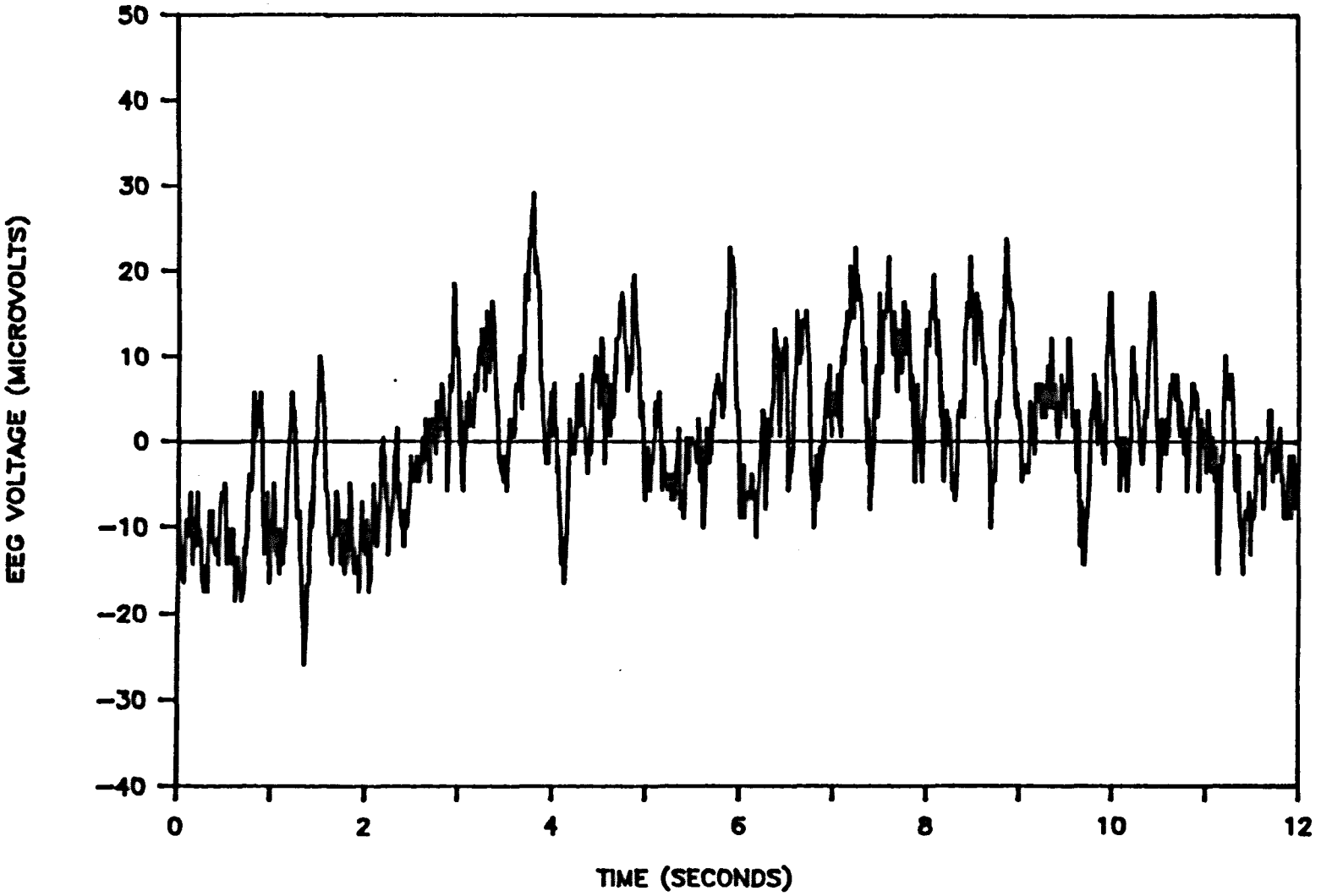

Figure 2.11 CNV response in an "at-risk" of Huntington's disease patient.

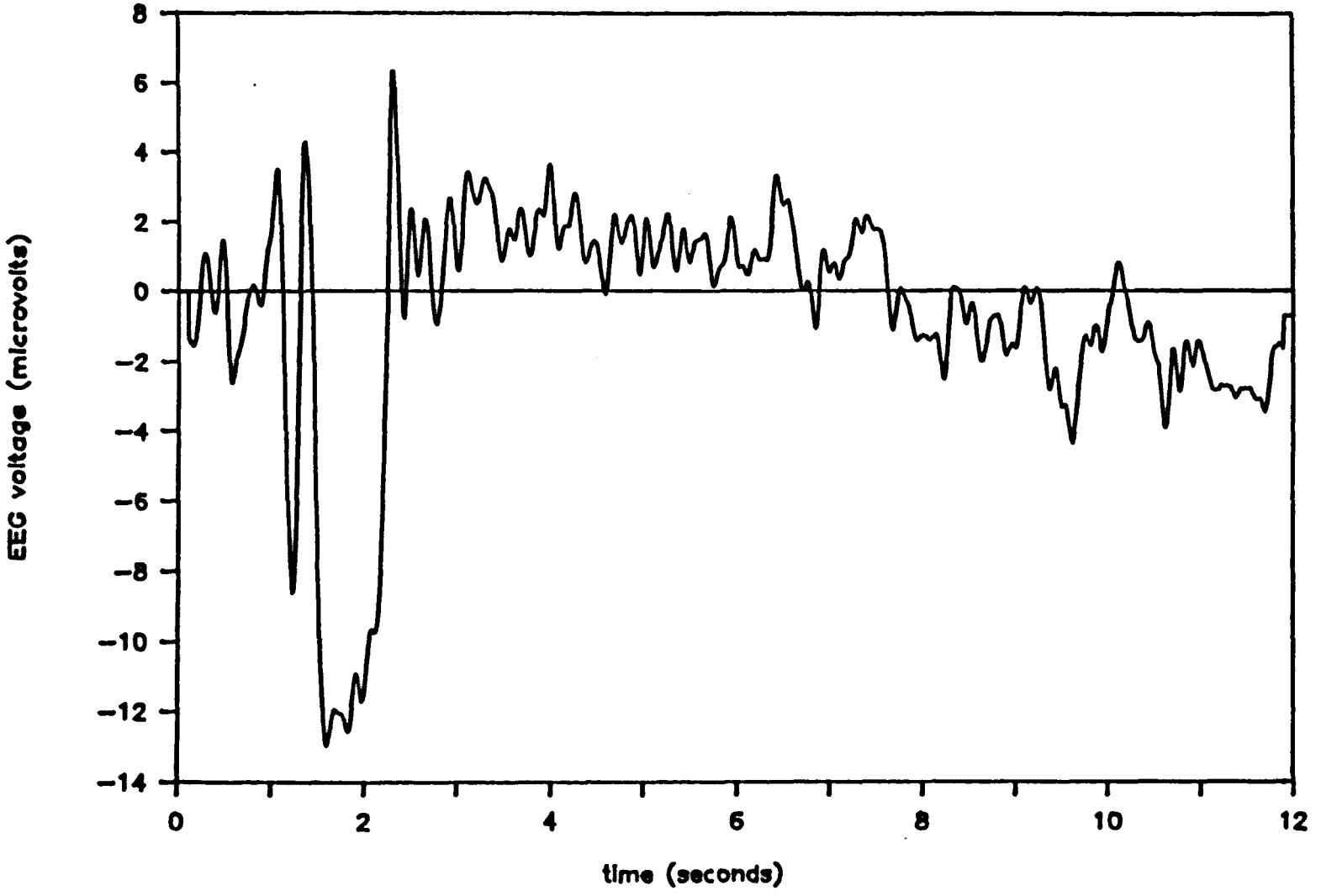

Figure 2.12 The preprocessed averaged CNV response in a normal subject.

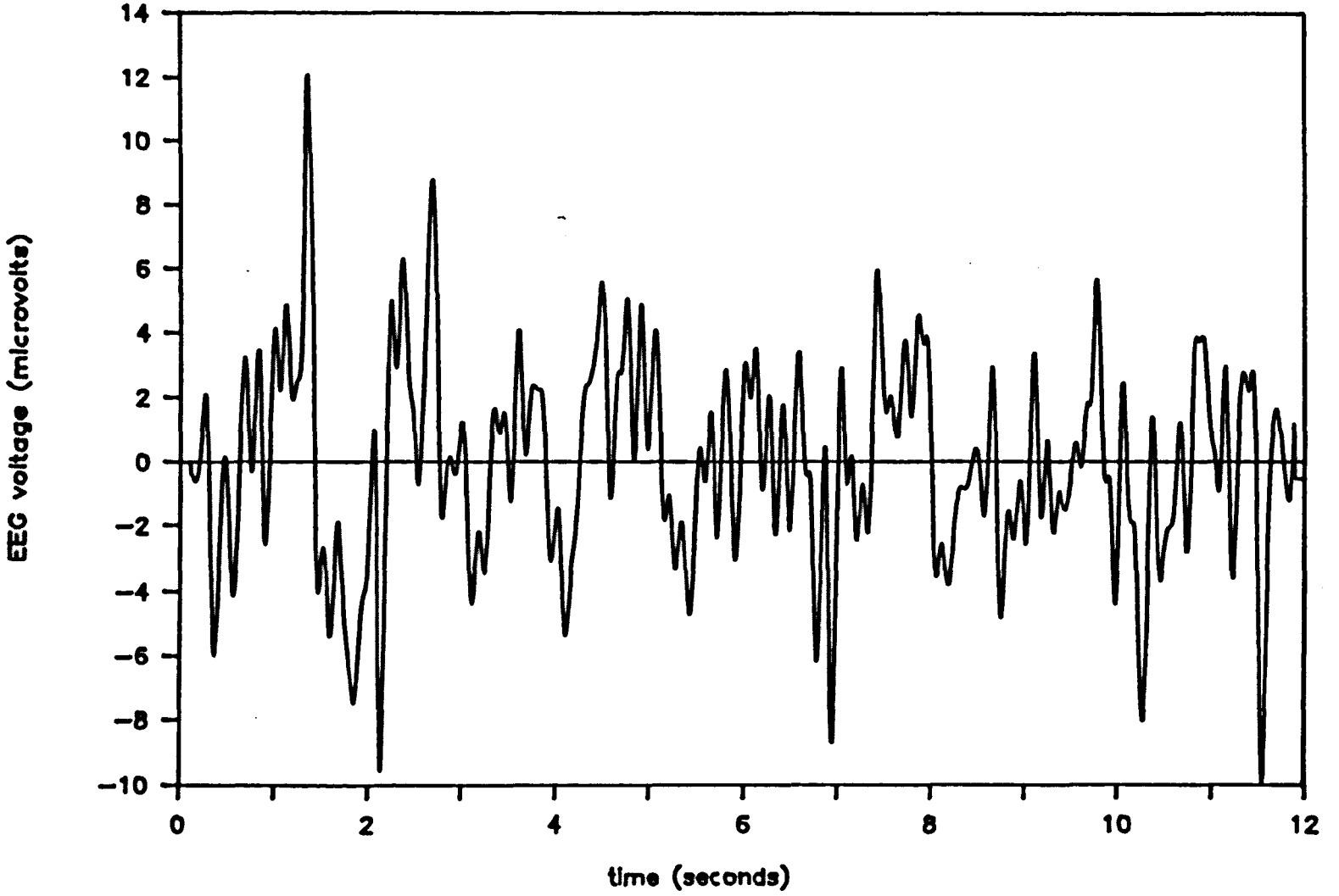

Figure 2.13 The preprocessed averaged CNV response in a Schizophrenic patient.

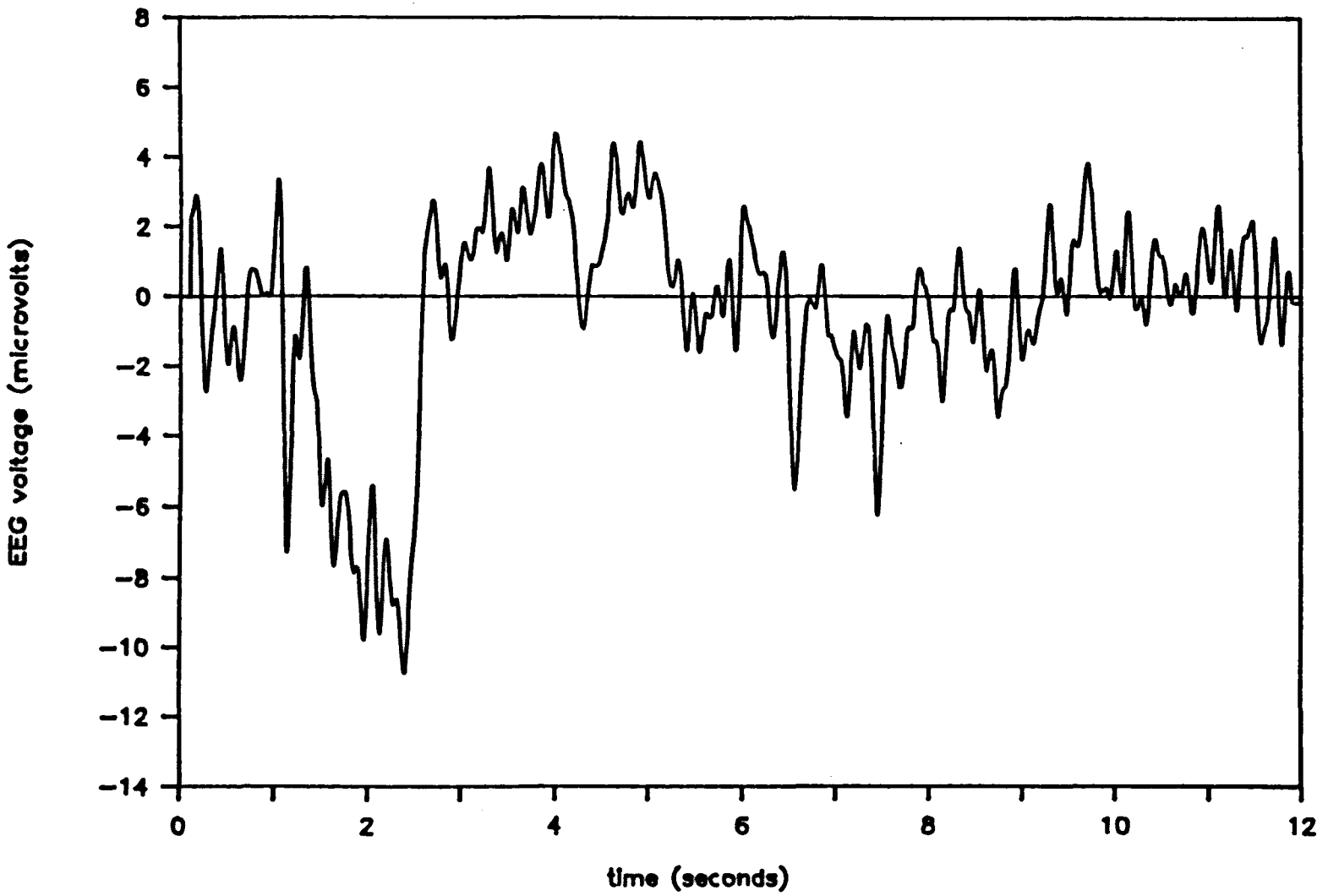

Figure 2.14 The preprocessed averaged CNV response in a Parkinson's disease patient.

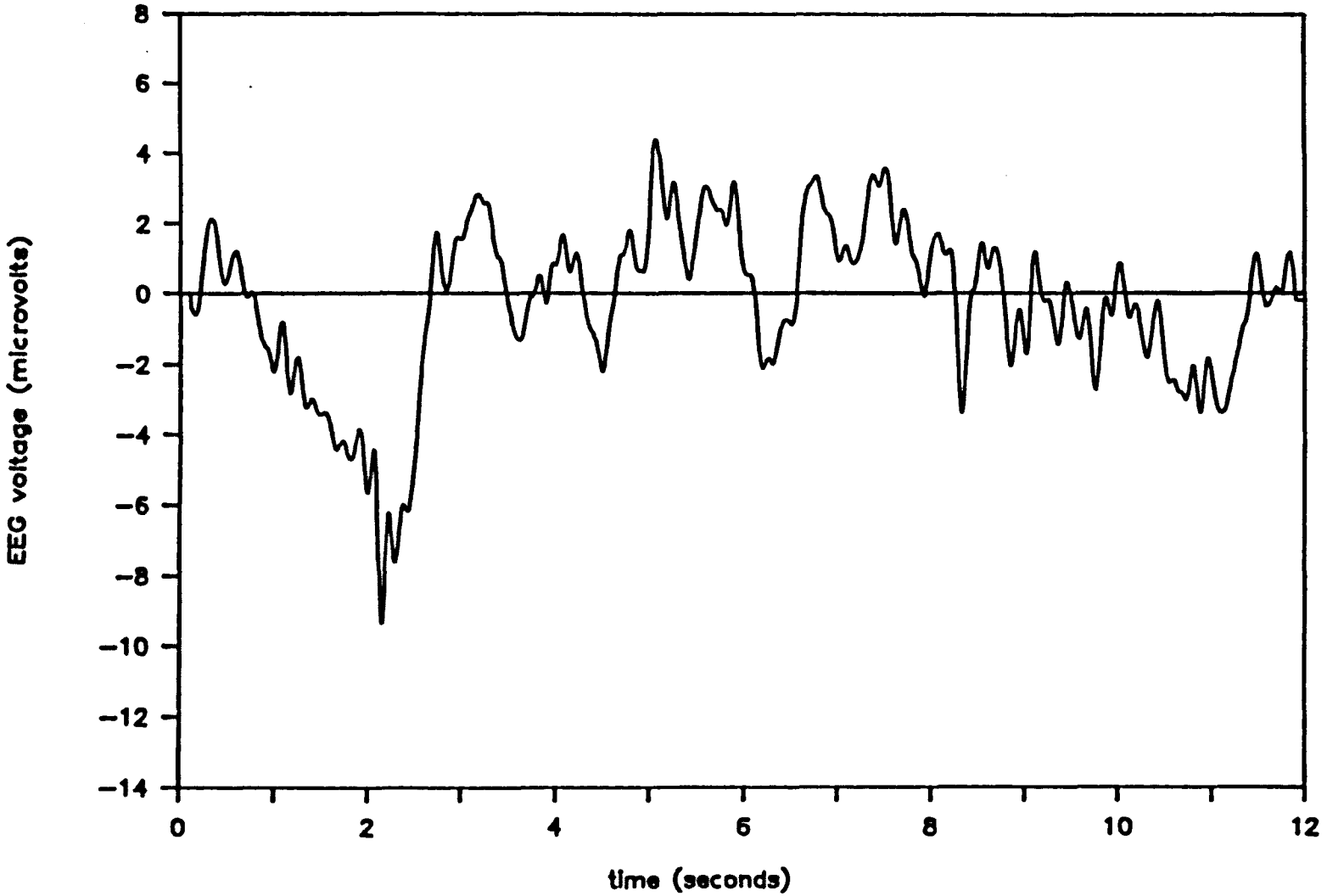

Figure 2.15 The preprocessed averaged CNV response in a Huntingon's disease patient.

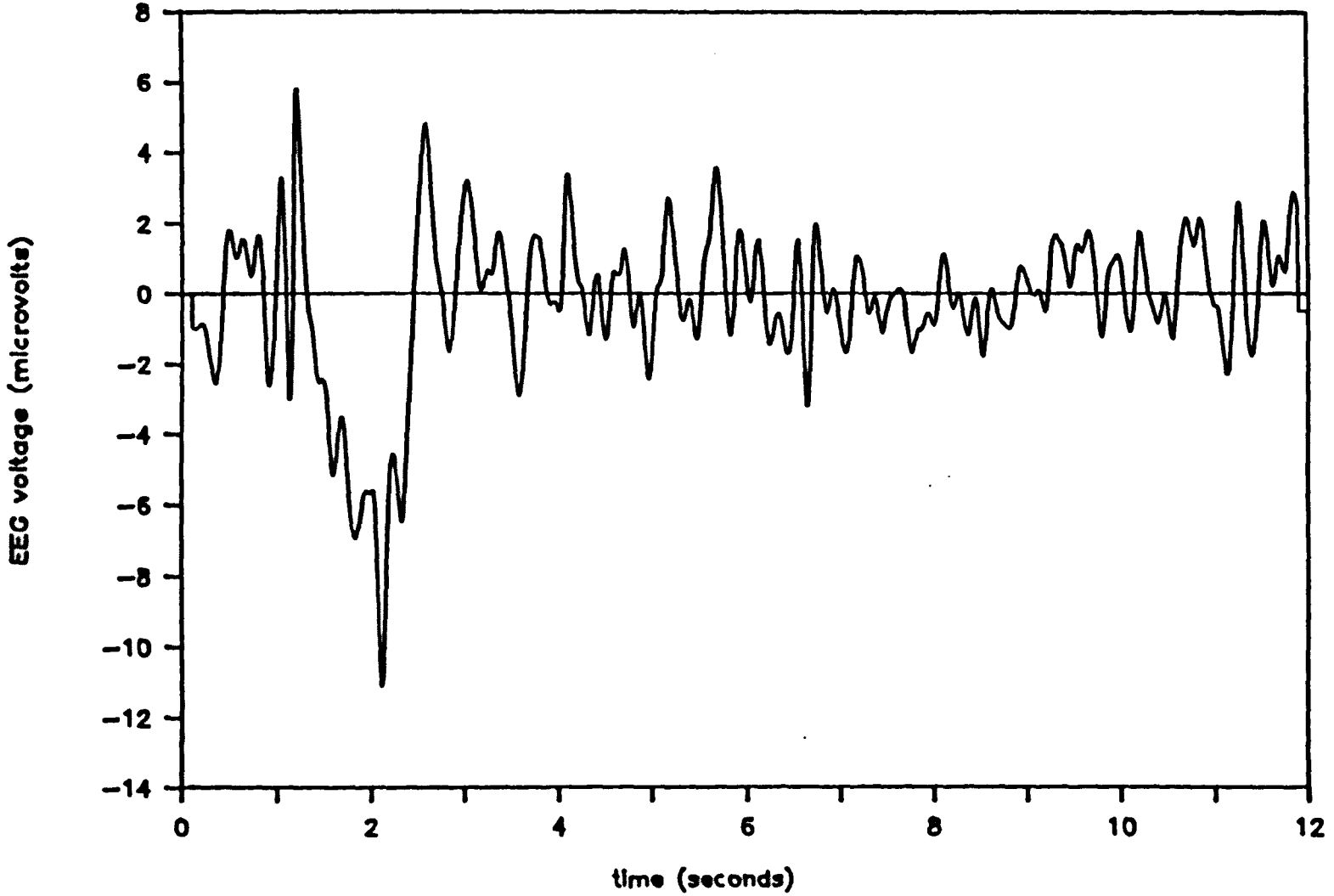

Figure 2.16 The preprocessed averaged CNV response in an at-risk of Huntington's disease patient.

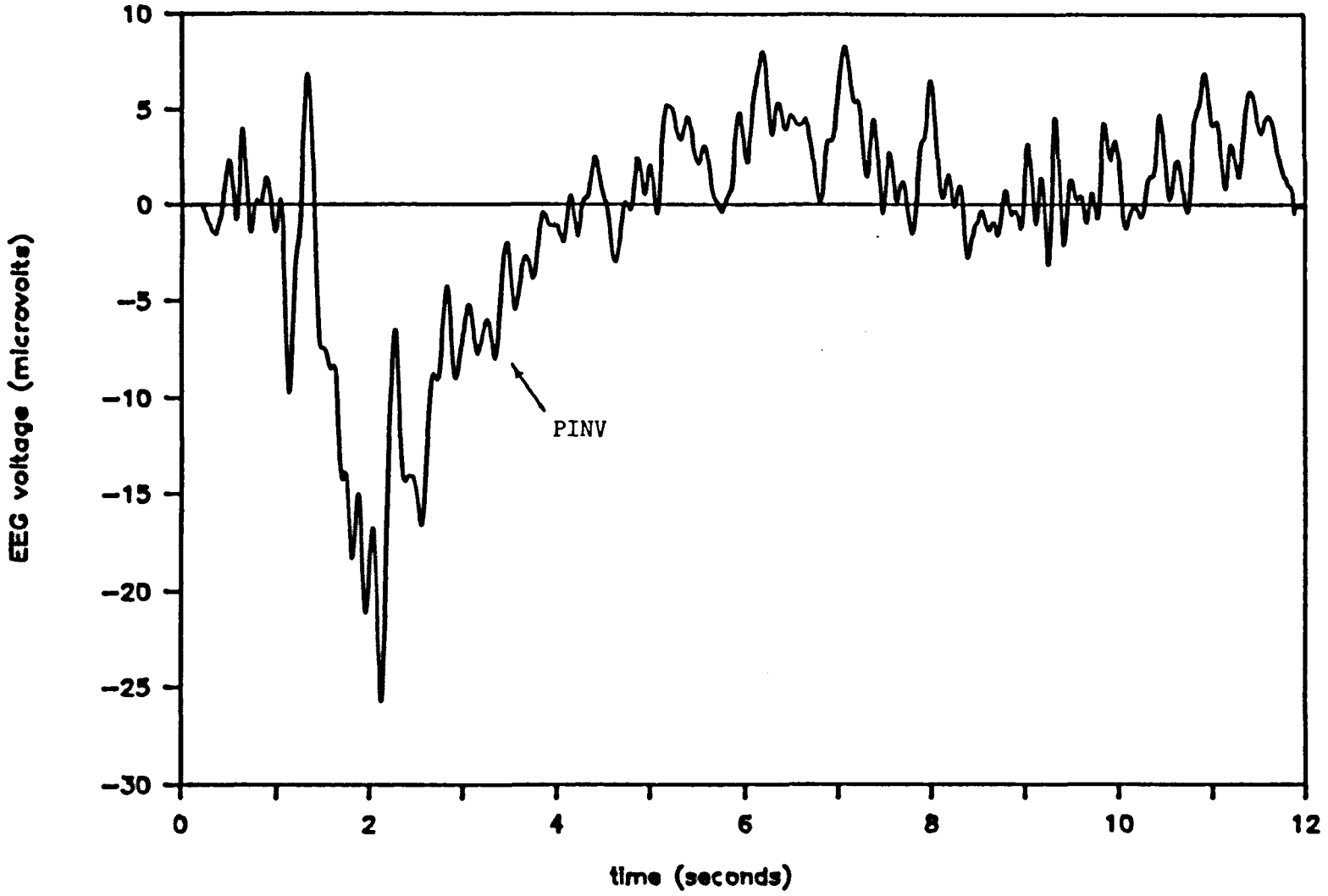

Figure 2.17 The PINV in a Parkinson's disease patient.

brain-behaviour functions [Tecce, 1972].

2.3 Review of the Relevant Studies in Event-Related Potentials

There have been numerous applications of ERPs in the medical field. Chiappa [1990] and Picton [1988] have provided a review of some of their applications. Although only the CNV was used in this study, whenever appropriate, the results of other relevant ERPs studies in schizophrenia, PD and HD are also included.

2.3.1 Event-Related Potentials in Schizophrenic Patients

The P300 amplitude has been reported to be significantly reduced in schizophrenic patients [Roth et al. 1980] [Pfefferbaum et al. 1984] [Barrett et al. 1986] [Blackwood et al. 1987] [Romani et al. 1987] [Pfefferbaum et al. 1989] [Ward et al. 1991]. A prolonged P300 latency has been reported by Pfefferbaum et al. [1984], Blackwood et al. [1987] and Romani et al. [1987].

P50 is a positive wave occurring 50ms after the onset of an auditory stimulus (such as a click). In an experiment Waldo et al. [1988] presented a series of pairs of clicks to 13 schizophrenic patients and 32 normal subjects (each click pair generated two P50 waves). They reported that in normal subjects, the P50 wave generated as a result of the second stimulus was diminished compared with the P50 generated as a result of the first stimulus. This phenomenon was not observed in schizophrenic patients. Other alterations of auditory ERPs in schizophrenic patients include a reduced N100 amplitude [Waldo et al., 1988] and a reduced P200 amplitude [Shenton et al., 1989].

Several studies have reported that the amplitude of the CNV in schizophrenic patients was significantly reduced compared with normal control subjects [Abraham et al., 1976] [Timsit-Berthier et al., 1984]. More recently, Abraham [1989] confirmed this finding by comparing the CNV amplitudes of 29

schizophrenic patients and 52 normal control subjects. Several studies have shown the presence of longer than normal PINV in the majority of schizophrenic patients [Roth, 1977] [Dubrovsky and Dongier, 1976] and there has also been evidence of abnormal PINV in schizophrenic children [Strandburg et al., 1984].

2.3.2 Event-Related Potentials in Parkinson's Disease Patients

The P200 and P300 components of auditory and the P100 component of visual ERPs in 20 PD patients and 20 normal control subjects were studied by Hansch et al. [1982]. They reported that in the case of PD patients the latencies of both the P200 and P300 components were significantly increased and the amplitude of the P100 component was significantly increased. Goodin and Aminoff [1986] analysed the N200 and P300 components of AEPs in 13 PD patients and 40 normal control subjects and reported a significant prolongation in the latencies of the N200 and P300 components in the PD patients. The amplitude of the VEP in 9 PD patients was reported to be significantly different from that of 12 age-matched normal control subjects [Calzetti et al., 1990]. Tachibana et al. [1988] studied the SEPs in PD patients and their normal subjects and found that the latency of the N20 component in the PD patients was significantly abnormal.

Dick et al. [1989] studied the Bereitschafts potential in 14 PD patients and 12 age-matched normal control subjects and reported that the amplitudes of the early components of the Bereitschafts potential were smaller in the PD patients. McCallum et al. [1970] observed a general reduction in the CNV amplitude in PD patients. This finding was later confirmed by Cohen [1974].

2.3.3 Event-Related Potentials in Huntington's Disease Patients

The SEPs in HD patients and AR of HD patients were investigated and compared with those of normal control subjects in several studies. An increase in latency

[Oepen et al., 1982] [Josiassen et al., 1982] and a reduction in amplitude [Noth et al., 1984] [Ehle et al., 1984] [Bollen et al., 1985] [Abbruzzese et al., 1990] of some SEP components were generally observed in HD patients. Josiassen et al. [1982] and Noth et al. [1984] also reported that some AR of HD patients exhibited amplitude reduction in their SEPs similar to that observed in HD patients, although the reduction tended to be smaller in the AR of HD patients.

Oepen et al. [1982], Josiassen et al. [1984] and Hennerici et al. [1985] have reported that the VEPs components in HD patients and some AR of HD patients were significantly reduced.

The auditory evoked potentials (AEPs) in 21 HD patients and 21 normal control subjects were analysed by Josiassen et al. [1984]. They reported the amplitudes of the AEPs components in HD patients were generally reduced.

Rosenberg et al. [1985] compared the P300 components of both auditory and visual ERPs in 13 HD patients with those in normal subjects. Nine HD patients had abnormal auditory P300 latencies and 10 HD patients had abnormal visual P300 latencies. Goodin and Aminoff [1985] analysed the latencies of the N200 and P300 components of AEPs in 13 HD patients and 40 normal control subjects. They found a significant prolongation in the latency of both the N200 and P300 components in HD patients compared with those of normal control subjects. Hömberg et al. [1986] studied the P200, N200 and P300 components of AEPs in 30 HD patients, 40 AR of HD patients and 60 normal control subjects. They reported that the latencies of the P200, N200 and (especially) P300 components were prolonged in the majority of HD patients and to a lesser extend in AR of HD patients.

Jervis et al. [1984] and [1989] reported that statistically significant differences

existed between the amplitude of some CNV harmonic frequency components in 8 HD patients and those of 6 normal subjects (an account of these studies is included in chapter 7).

Josiassen et al. [1988] studied the SEPs, VEPs and AEPs in 22 individuals AR of HD and reported that the generalised reduction in the amplitude of EPs in AR of HD patients was not due to emotional symptoms associated with knowledge of AR status. They suggested that the amplitude changes might reflect early and subtle changes of an organic nature.

2.4 The Possible Effects of Medication on Event-Related Potentials

Some of the patients included in this study were on medication related to their disorders. The possible effects of medication on ERPs have been investigated in several studies. Josiassen et al. [1984] reported that medication might further reduce the already lower than normal amplitude in the auditory and visual EPs in HD patients. Blackwood et al. [1987] found that the latency of the P300 component in auditory ERPs obtained from unmedicated schizophrenic patients was significantly prolonged and remained unchanged after a long term follow up of the patients on medication. They also reported that the amplitude of the P300 component was reduced in schizophrenic patients not on medication and remained reduced following neuroleptic drug treatment. Ward et al. [1991] reported a reduced P300 amplitude in unmedicated schizophrenic patients. The amplitude and latency of VEPs in unmedicated PD patients compared to normal subjects were also significantly different according to Calzetti et al. [1990].

2.5 Conclusion

The articles reviewed in this chapter indicate schizophrenia, PD and HD cause structural brain abnormalities and some changes in the ERPs. The CNV was

described and the reasons for selecting this potential for detecting schizophrenia, PD and HD were discussed.

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Chapter 3 Description of the Instrumentation System

In this chapter the instrumentation system used for data recording is described. An instrumentation system was required for simultaneous recording of the signals from eight analogue channels, to generate the stimuli necessary for recording of the CNV and to measure the subjects' reaction times to an acoustic stimulus. The signals of interest were the CNV (from two sites), electro-oculogram (EOG) (from four sites), electrocardiogram (ECG) and psychogalvanic response (PGR). The magnitudes of these signals varied from a few microvolts to several millivolts. To increase the accuracy of digitisation of the signals a programmable gain amplifier (PGA) was required the gain of which could be software adjusted in accordance with the magnitudes of the signals. The system had to provide a sufficient data storage facility (about 1 megabytes per subject), and also had to process and analyse the data. An online paper chart recording of the signals was necessary to observe the signals during the recording and to have a hard copy of the data for future reference. It was important to minimise distortion of the signals during the acquisition, storage and processing. Portability, reliability, the cost of the instrumentation system, and patients' safety during the data recordings were also design considerations.

The commercially available recording systems, such as analogue magnetic tapes, were not suitable as they did not meet the required specifications. Therefore a PC-based instrumentation system was developed. The system consisted of an IBM PC (AT model, with a 20 megabytes hard disk and fitted with a Sysgen tape steamer), an Elema-Schönander EEG machine, an acoustic stimulator and a signal conditioning unit. The set-up of the system during a recording session is shown in Figure (3.1).

The recorded CNV from one of the sites, the ECG data and the PGR data were not analysed during the course of this study and they were left for future studies.

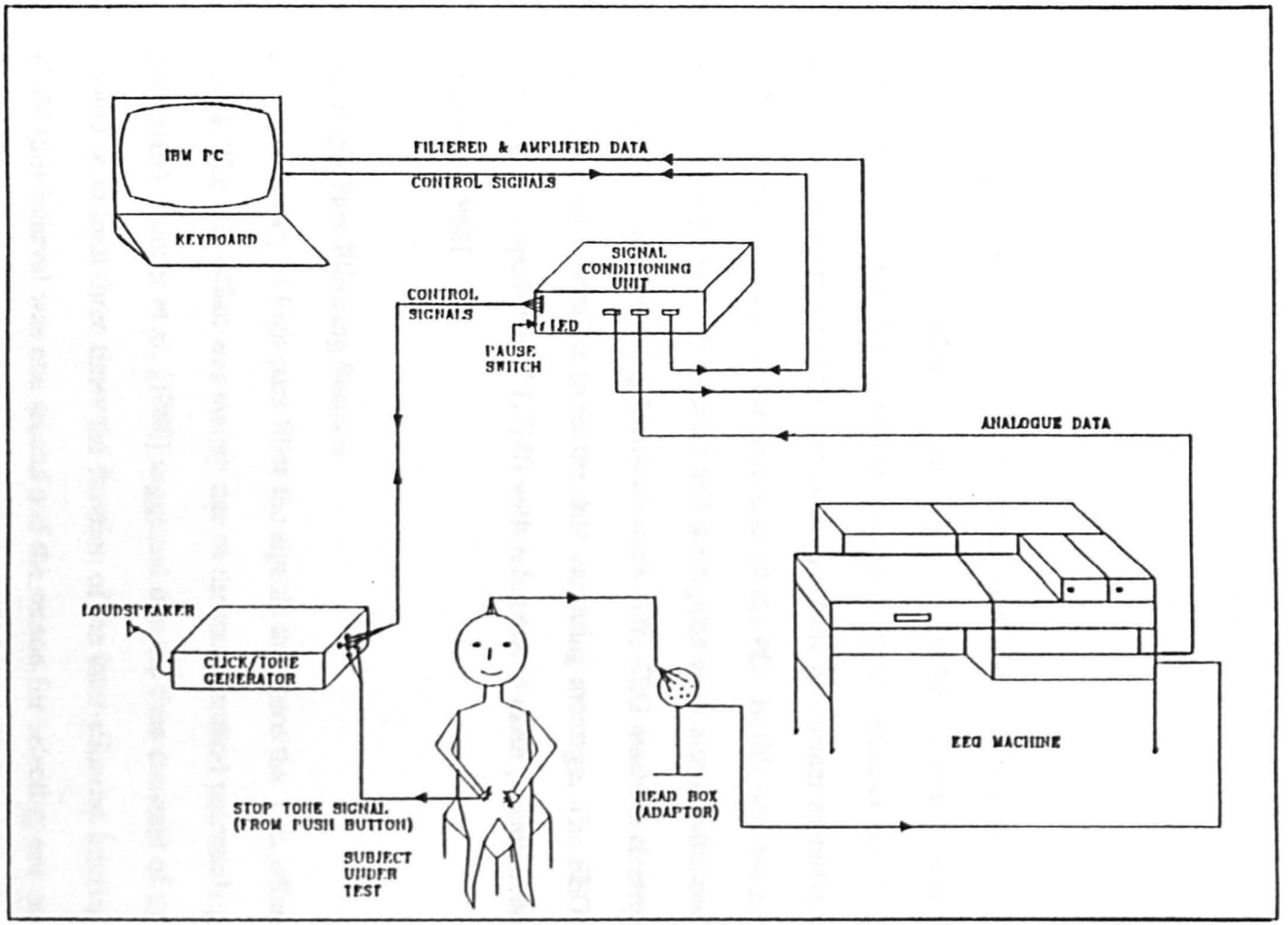


Figure 3.1 The set-up of Instrumentation System during a data recording session.

3.1 The Instrumentation System Input Stage

The signals from the electrodes were fed via the head-box (adaptor) into the electrode selector switches and the differential amplifiers of the EEG machine as shown in Figure (3.2). Each of these differential amplifiers had a fixed gain of 50. Differential recording was necessary for compatibility with differential measurements between the electrode pairs and in order to attenuate the common mode noise.

The analogue signals from the outputs of the differential amplifiers followed two paths. The first path led to the next section in the EEG machine, while the second path led to a 25-way D-type connector. The D-type connector was coupled to the section of the instrumentation system responsible for further amplifying, digitising and storing of the data on the hard disk of the PC. In this way the EEG machine provided the paper chart as usual and the signals were also conditioned, digitised and stored by the following hardware units. The EEG machine electrode selector switches made it possible to set the data recording montage. The EEG machine had an input impedance of 1.7MΩ with reference to earth [Elema-Schönander databook, 1968].

3.2 High-Pass Filtering Section

It was necessary to high-pass filter the signals to reduce the d.c. offset in the signal. The d.c. offset was mainly due to the extracerebral potentials (eg. skin potentials). Cooper et al. [1980] suggested that the time constant of this filter should be at least three times the duration of the inter-stimulus interval (ISI) of the CNV (this interval was one second and the reason for selecting one second for this period is given in chapter 5) to avoid distortion of the CNV. A first order lead network with $C=10\mu F$ and $R=1M\Omega$ was used for this purpose. This circuit had a time constant of ten seconds. This corresponded to a cut-off frequency (f_c) of

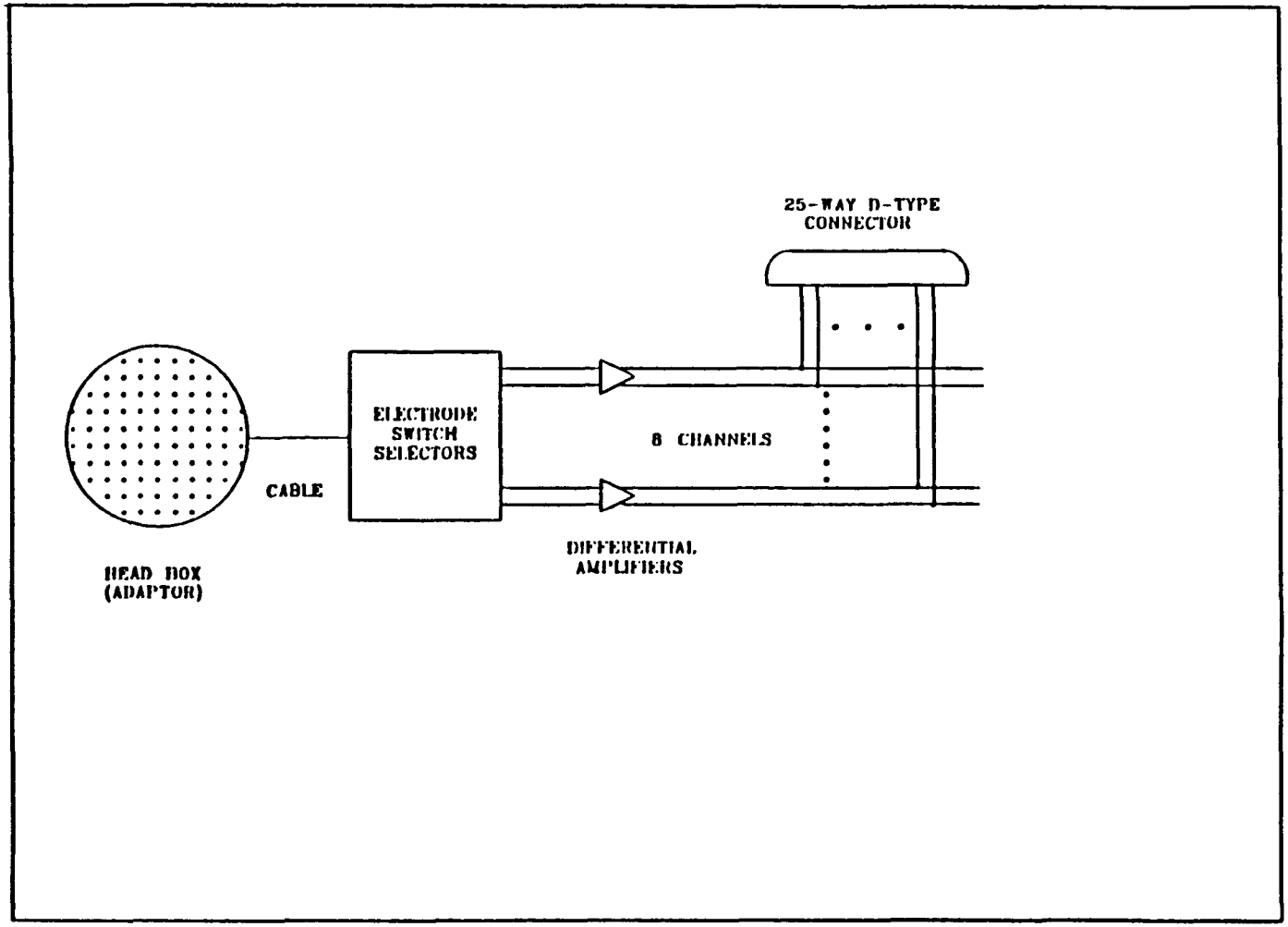


Figure 3.2 Instrumentation system input stage.

0.0159Hz, where,

$$f_c = \frac{1}{2\pi RC} \qquad \ldots(3.1)$$

3.3 Second Stage Amplification Section

There was an instrumentation amplifier for each channel following the high-pass filter section as shown in Figure (3.3). The function of each instrumentation amplifier was to further amplify and to convert its input signal to an unbalanced form. The instrumentation amplifier type was INA110 [Burr-Brown, 1986]. The INA110 device is a monolithic FET input device. It was selected because it had a high common mode rejection ratio (about 106dB), low gain drift, low offset drift (2μV/deg.C), fast settling time (4μs to 0.01%) and easily adjustable gain. The instrumentation amplifier circuit is shown in Figure (3.4). A fixed resistor (R_{GF}) and a potentiometer (R_{GV}) were placed in series between pin 3 and pin 16 (the pins 11, 12, and 16 were connected together). The net resistance of R_{GF} and R_{GV} (ie. $R_{GV} + R_{GF}$) was referred to as R_G. The value of R_G determined the gain of the instrumentation amplifier and it was calculated using [Burr-Brown, 1986],

$$R_G = \frac{40000}{Gain - 1} - 50\ \Omega \qquad \ldots(3.2)$$

For channels 1 to 6 (allocated for EEG and EOG recordings) the instrumentation amplifier gain was 52.5. It was necessary to adjust the R_{GV} potentiometer to obtain this gain. For channels 7 and 8 (allocated for the ECG and PGR recordings), the instrumentation amplifier gain was set to 2.6. This was achieved by placing a 10kΩ potentiometer in series with a 20kΩ resistor between pins 3 and 16.

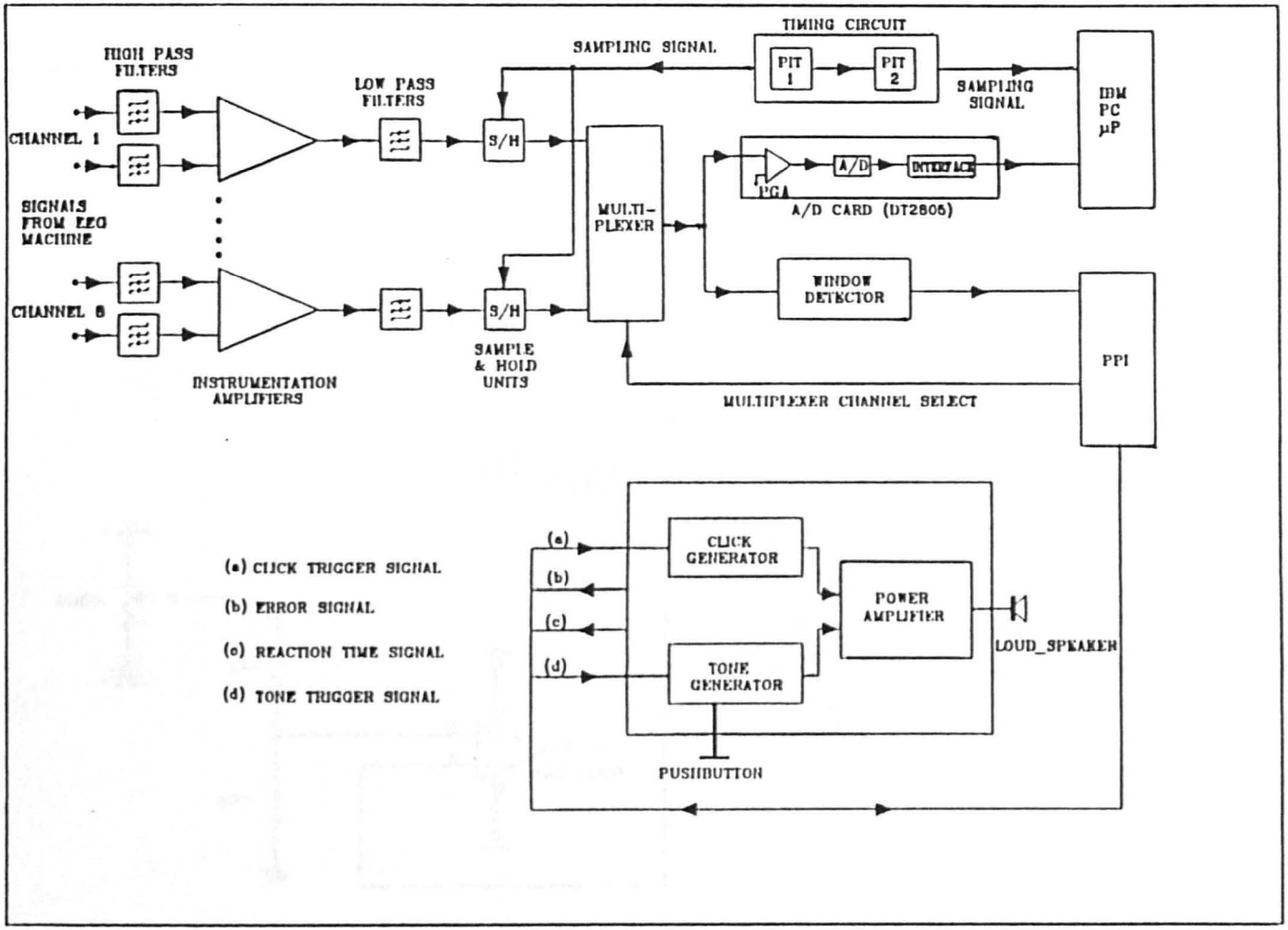


Figure 3.3 The Sections of the instrumentation system following the input stage.

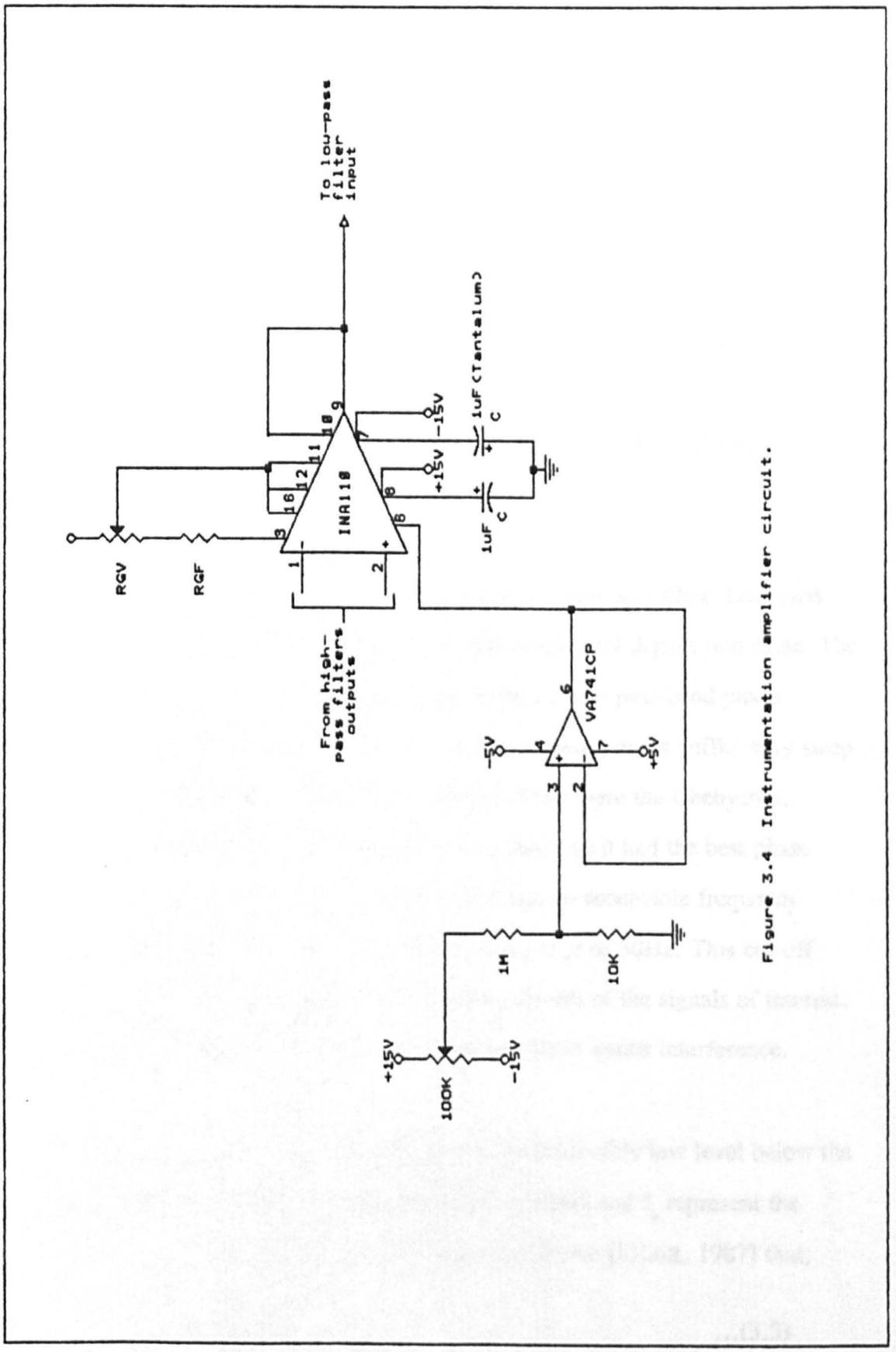


Figure 3.4 Instrumentation amplifier circuit.

The instrumentation amplifier gains were decided after considering the amplitude range of each input signal and the gains provided by the other amplifiers in each channel (this is described in section 3.8).

As the passive components attached to one input of each instrumentation amplifier were not completely matched with components at the other input (ie. the resistors and capacitors had a tolerance), a small d.c. offset appeared at the output of each instrumentation amplifier. This offset was zeroed by applying a voltage to the voltage reference pin (pin 6) of each instrumentation amplifier through a buffer. This method of adjusting offset has been described in Burr-Brown [1986].

3.4 Low-Pass Filtering Section

Following each instrumentation amplifier there was a low-pass filter. Low-pass filtering was necessary to prevent aliasing in the subsequent digitisation stage. The design considerations for the low-pass filters were a linear pass-band phase response, a sufficiently flat pass-band frequency response, and a sufficiently steep gain roll-off. Three filter types were considered. They were the Chebyshev, Butterworth and Bessel. The Bessel filter was selected as it had the best phase response among the three filter types and it also had an acceptable frequency response. It was decided to use a cut-off frequency (f_{c1}) of 30Hz. This cut-off frequency was several times higher than the frequencies of the signals of interest. The low-pass filtering process also attenuated any 50Hz mains interference.

Any aliasing component has to be attenuated to an acceptably low level below the pass-band components. Let f_r denotes this aliasing signal and f_s represent the sampling frequency (see Figure (3.5)). It has been shown [Elliott, 1987] that,

$$f_s = 2f_{c1} + f_t \qquad \ldots(3.3)$$

where

$$f_t = f_r - f_{c1} \qquad \ldots(3.4)$$

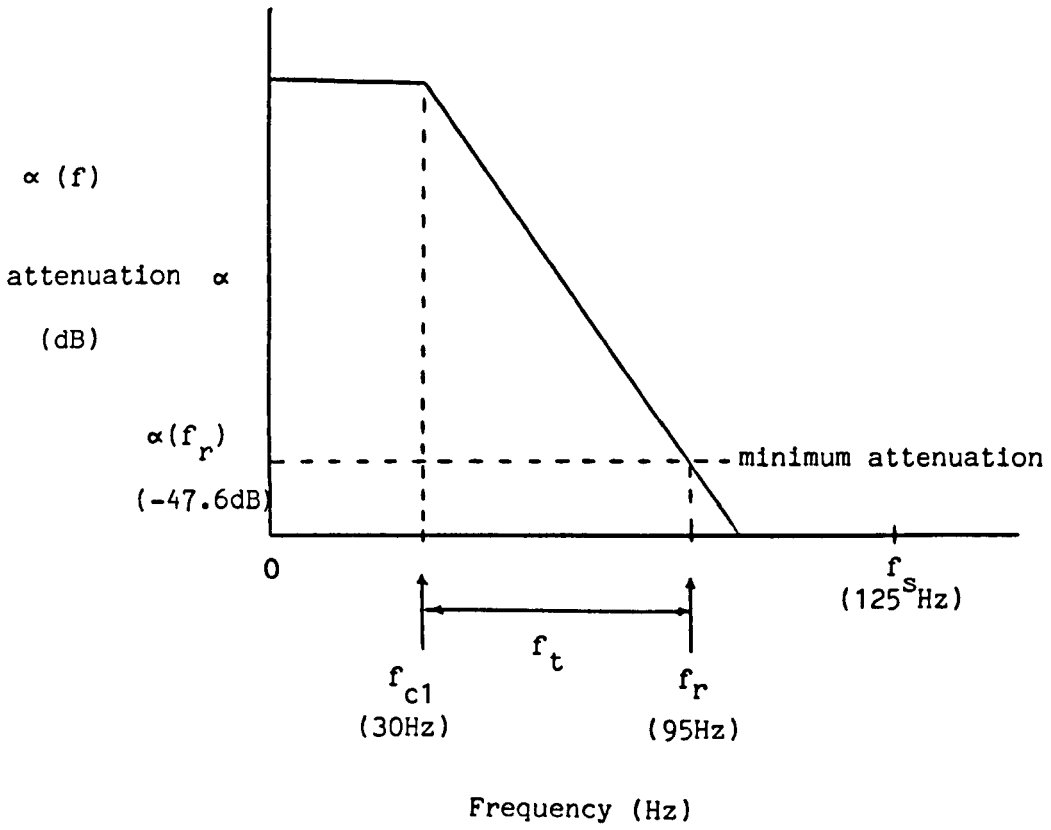


Figure 3.5 The method used to identify highest aliasing frequency component.

therefore $f_r = f_s - f_{c1}$ ...(3.5)

For f_s=125Hz (see section 3.5 for information related to sampling frequency) and f_{c1}=30Hz, the value of f_r is 95Hz.

It was decided to use a fourth order filter. The attenuation (dB) for a fourth order Bessel low-pass filter at a frequency f is given by [Van Valkenburg, 1984],

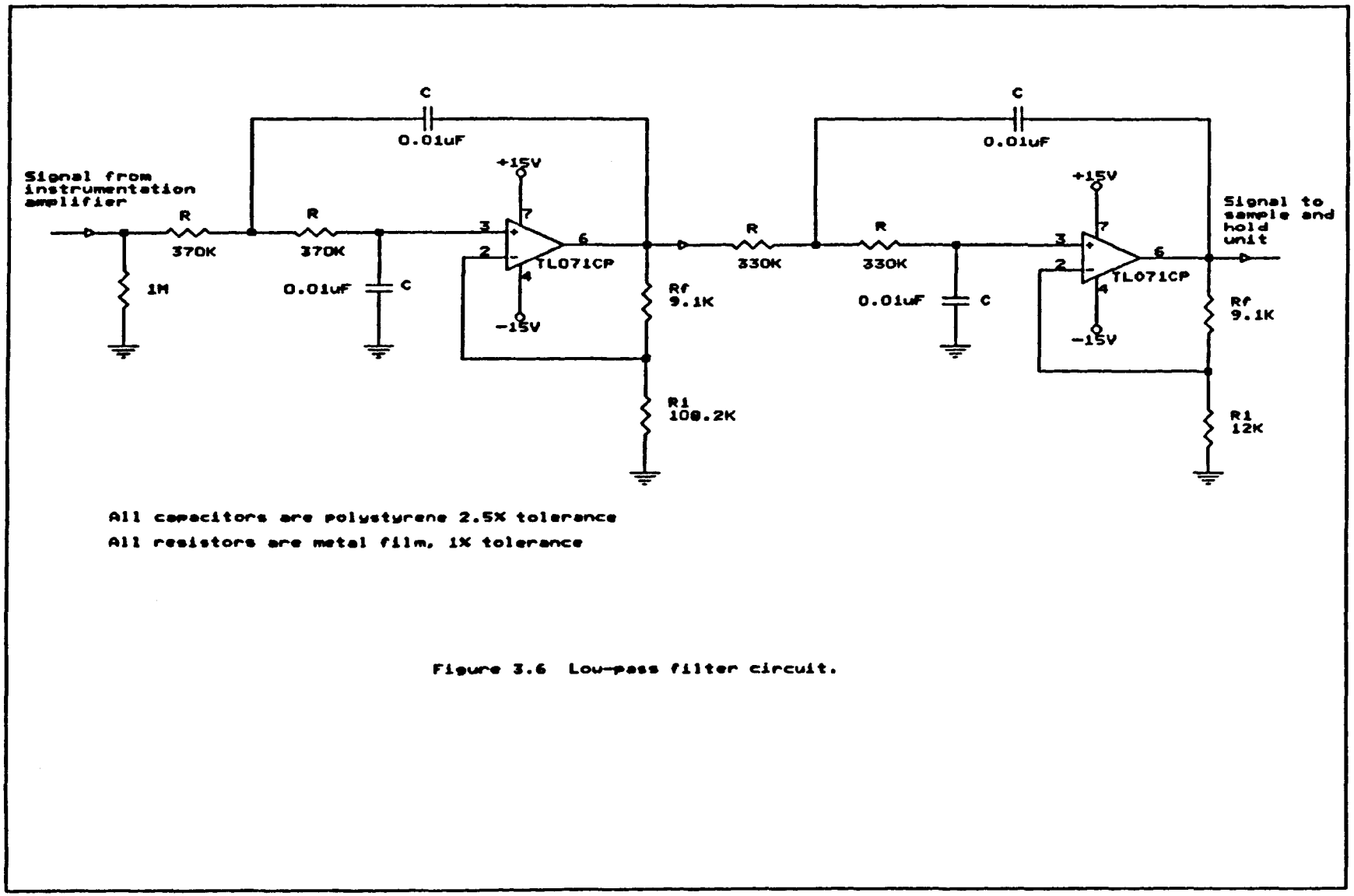
$$\alpha(f) = 20\log_{10}\left[\frac{1}{s^4+10s^3+45s^2+105s+105}\right] \text{ (dB)} \qquad \ldots(3.6)$$

where $s=jf/f_{c1}$. For largest aliasing component (ie. f_r=95Hz), s=j95/30. Substituting s=j95/30 in (3.6) gives an attenuation of -47.6dB. This attenuation of the largest aliasing component was considered sufficient.

The low-pass filter circuit was based on the voltage-controlled voltage source (VCVS) filter. The VCVS is a variation of the Sallen and Key filter [Chen, 1982]. The circuit diagram of the low-pass filter is shown in Figure (3.6). The values of the resistor (R) and the capacitor (C) were calculated using,

$$RC = \frac{1}{2\pi f_n f_{c1}} \qquad \ldots(3.7)$$

where f_n is the normalising factor. The values of the f_n for the first and second stages of the fourth order Bessel filter were 1.432 and 1.606 respectively [Horowitz and Hill, 1987]. The values of R_1 and R_f were calculated using,



All capacitors are polystyrene 2.5% tolerance

All resistors are metal film, 1% tolerance

Figure 3.6 Low-pass filter circuit.

$$K = 1 + \frac{R_f}{R_1} \qquad \ldots(3.8)$$

where k is the voltage gain. The values of k for the first and second stages of the filter were 1.084 and 1.759 respectively [Horowitz and Hill, 1987]. This resulted in the filter gain of 1.907 (ie. 1.084 x 1.759).

The operational amplifier type used for this filter was TL0741CP. This type was selected because it had low noise and low distortion.

3.5 Sample and Hold Section

The signals from the eight channels were sampled simultaneously. This was because the removal of ocular artefact potentials from the CNV involved the correlation of the EEG and EOG signals and therefore it was important to maintain the phase relationship between the signals. A sample and hold (S/H) signal generated from the timing circuit (this circuit is described in section 3.9) was fed to the S/H unit of each channel resulting in the simultaneous sampling of the signals. The usual sampling rate for CNV recording is about 100Hz (for example, Prescott [1986] used a sampling rate of 100Hz in his CNV studies). The sampling rate used in this study was 125Hz. This also conformed with the sampling frequency used in previous studies [Nichols, 1982] [Coelho, 1988] and corresponded to a S/H period of 8ms (ie. 1/sampling rate), resulting in a multiplexing rate of about 1kHz.

The S/H device type was LF398. This device had a sufficiently fast acquisition time (less than 10μs), low output noise in hold mode and low droop rate [National Semiconductor, 1988]. The type and the value of the hold capacitor (C_H) were important as this capacitor determined the acquisition time and droop rate. A

0.01μF polystyrene capacitor was selected for C_H. The value of this capacitor provided an acceptable compromise between the acquisition time and droop rate and its type ensured a low dielectric absorption loss. The sample and hold circuit is shown in Figure (3.7).

3.6 Multiplexing Section

The output of the S/H unit from each channel was connected to an analogue multiplexer (type HI506) as shown in Figure (3.3). It was decided to use a 16-channel multiplexer (rather than an 8-channel multiplexer) to allow for any possible future expansion of the system. The multiplexer circuit is shown in Figure (3.8). The multiplexer channels were selected through a programmable peripheral interface (PPI) device (the PPI device is described in section (3.13)). The PPI device was TTL logic compatible. The multiplexer was a CMOS device. Therefore, a TTL to CMOS voltage level shifter (type CD40109B) was incorporated to interface the multiplexer with the PPI device.

3.7 Third Stage Amplification and Signal Digitisation Method

A DT2805 card from the DT2801 Data Translation series [1985] was available and it was used to further amplify and to digitise the signals. The cards had a programmable gain amplifier (PGA) and a 12-bit analogue to digital convertor (A/D). The PGA preceded the A/D and its gain could be software adjusted to 1, 10, 100 or 500. The conversion time of the A/D was 25μs. This was sufficiently fast for the multiplexing time of 1ms.

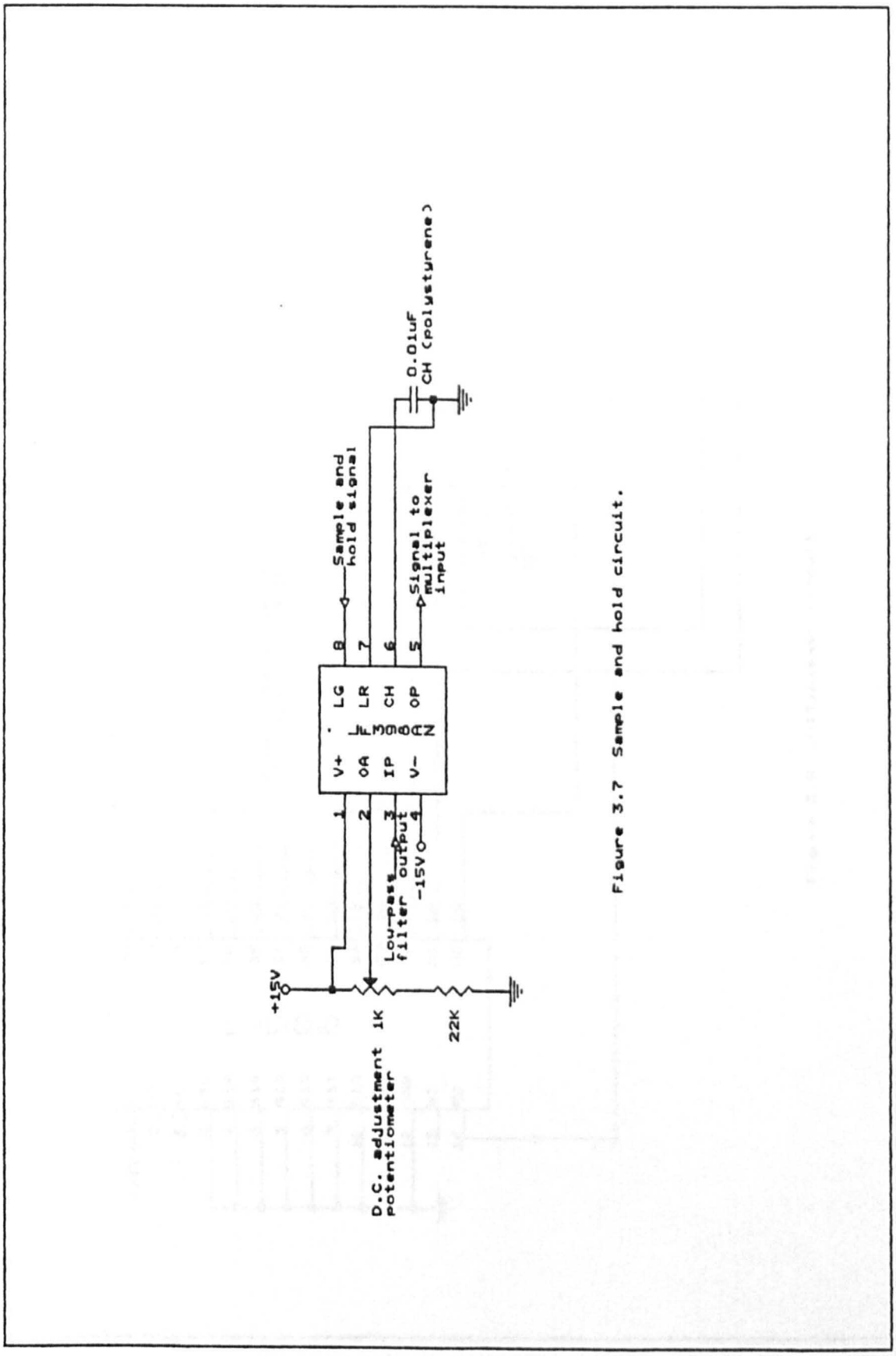


Figure 3.7 Sample and hold circuit.

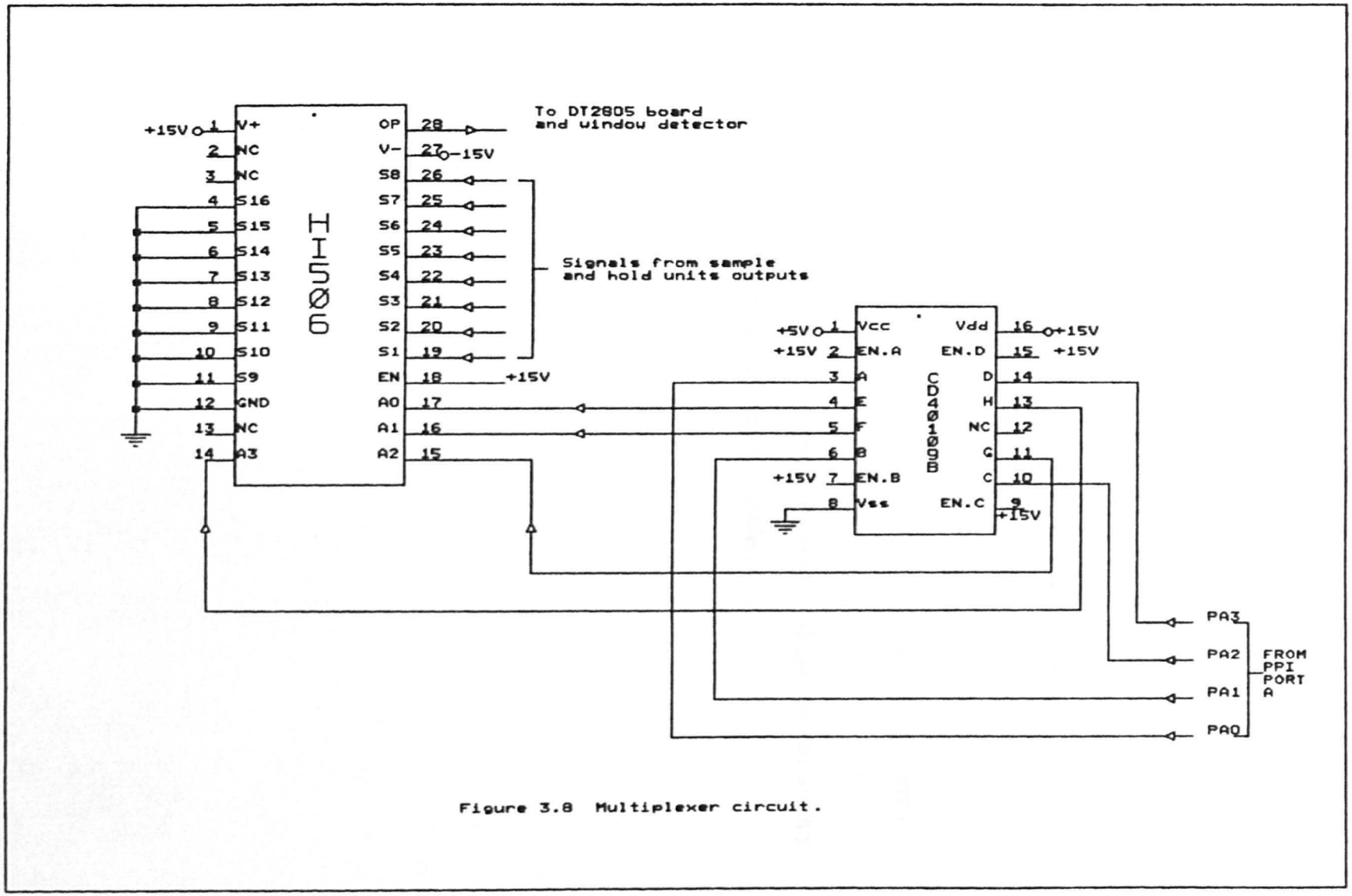


Figure 3.8 Multiplexer circuit.

The magnitudes of signals varied from a few microvolts (as in the case of the CNV) to several millivolts (as in the case of the PGR). To increase accuracy, before signal digitisation, the signal magnitude was estimated with the aid of a circuit known as a "window detector" (WD). The gain of the PGA was software adjusted after reading the WD output. The WD was designed to detect the threshold voltages of $\pm$20mV, $\pm$100mV, $\pm$1V and $\pm$10V. These threshold voltages corresponded to the PGA gains of 500, 100, 10 and 1 respectively. Each threshold voltage multiplied by its corresponding PGA gain resulted in A/D full scale range of $\pm$10V. The block diagram of the WD is shown in Figure (3.9) and the sections of its circuit are shown in Figure (3.10). The WD circuit composed of three pairs of comparators (type LM311). The inputs to each comparator were the multiplexer output and the relevant threshold voltage. The effect of varying the signal magnitude on the WD output is shown in Figure (3.11) and the relationship between WD output and PGA gain is shown in Table (3.1).

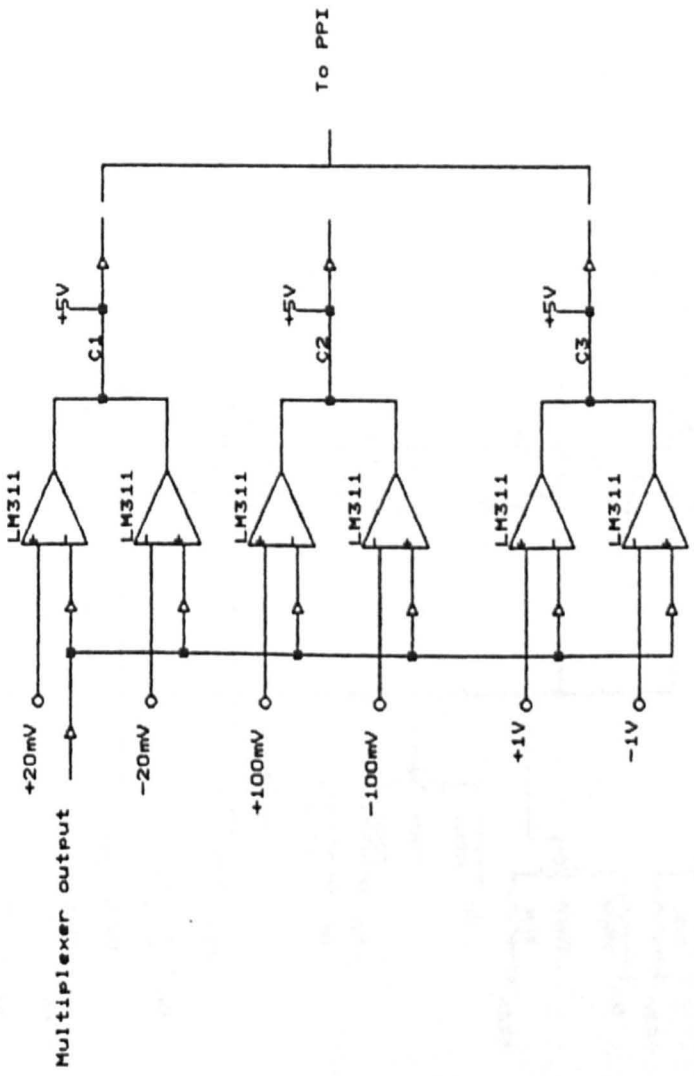


Figure 3.9 Block diagram of the window detector.

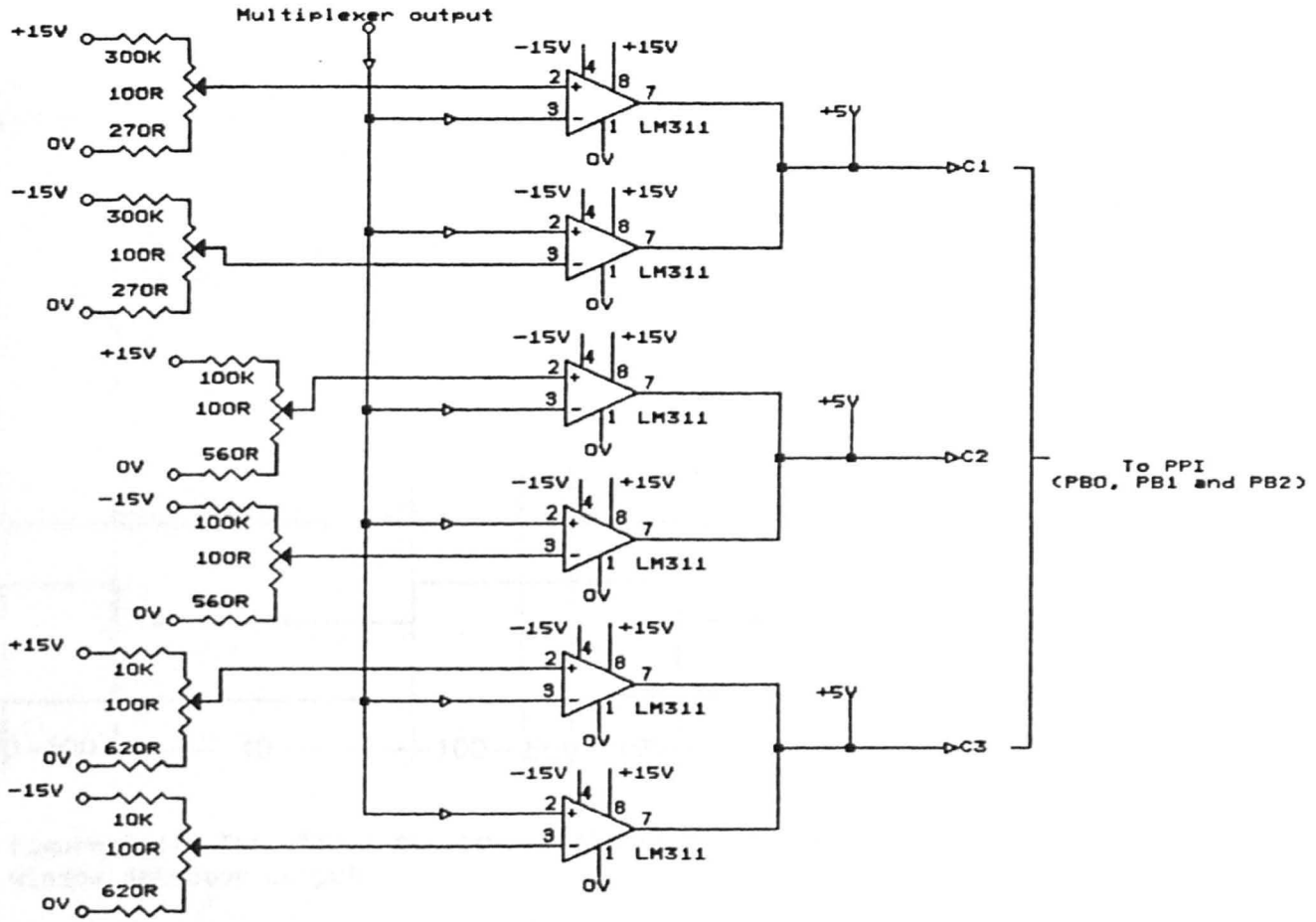


Figure 3.10 Window detector circuit .

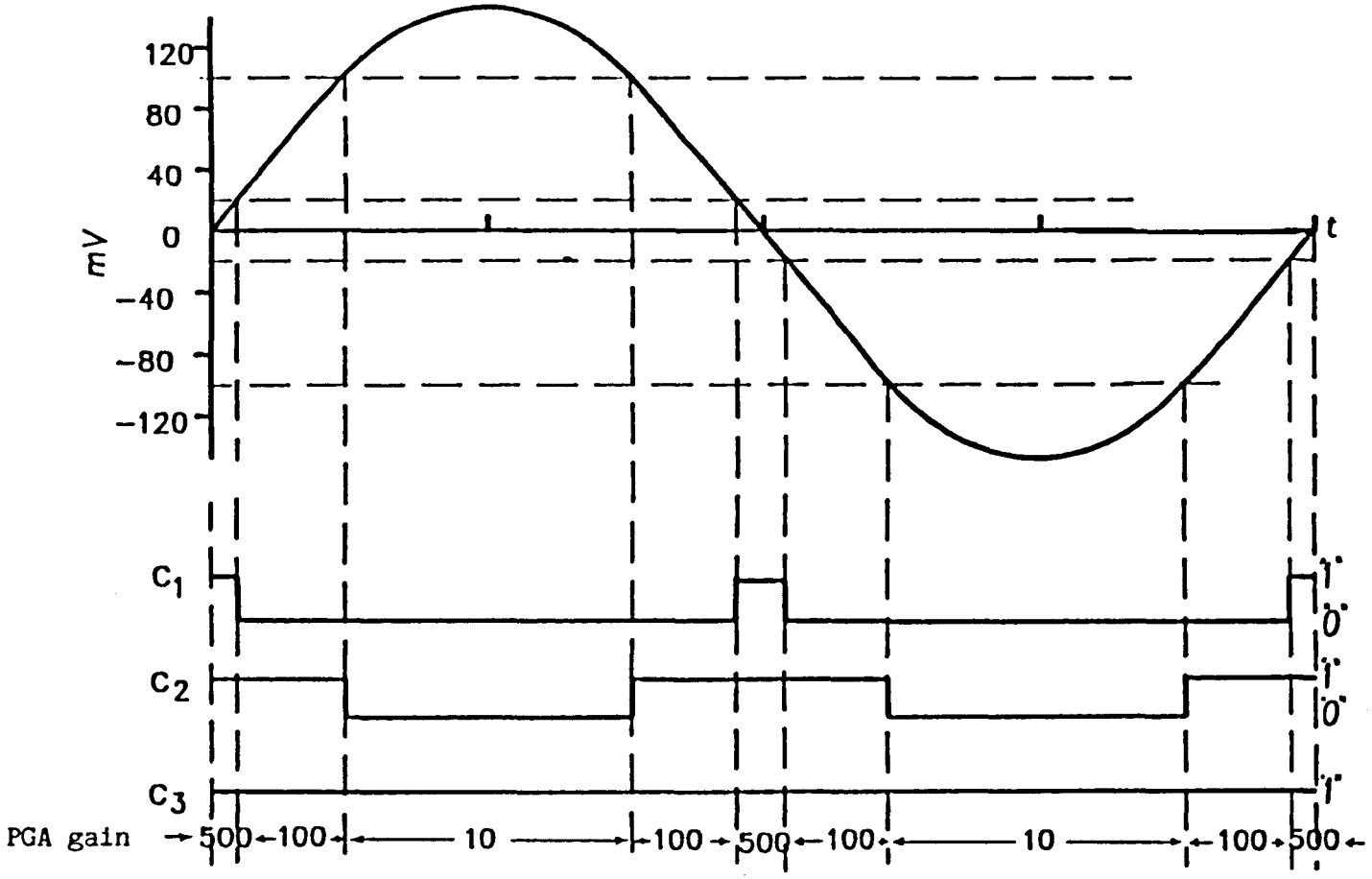


Figure 3.11 The effect of varying signal magnitude on the window detector output.

Table (3.1) WD outputs and the corresponding PGA gains.

Signal Range	C1	C2	C3	WD Output	PGA Gain
±1V to ±10V	0	0	0	0	1
±100mV to ±1V	0	0	1	4	10
±20mV to ±100mV	0	1	1	6	100
0V to ±20mV	1	1	1	7	500

When the magnitude of input signal ($|v_i|$) to the WD was less than the threshold voltage ($|v_r|$) for a comparator pair, the common output of that pair was logic "1". As $|v_i|$ exceeded $|v_r|$ the common output of the pair was logic "0".

After issuing a S/H signal the following steps were carried out: i) channel 1 of the multiplexer was selected, ii) the output of the WD was read through the PPI device, iii) the PGA gain was software adjusted to provide an appropriate gain (for example if the signal magnitude was below 20mV, the PGA gain was set to 500), iv) the signal was digitised, v) steps (i) to (iv) were repeated for channels 2 to 8.

The value of the WD output (which was 1 byte) was stored with the corresponding digitised signal (which was 2 bytes). Therefore each sample produced 3 bytes. When processing the data, the magnitudes of the signals were adjusted according to the WD outputs.

3.8 Total Gain Provided By Each Channel

The total gain provided by each channel was calculated using,

$$\text{Total gain} = G_1 \times G_2 \times G_3 \times G_4 \qquad \ldots(3.9)$$

where G_1 = first stage amplification (= 50),
G_2 = second stage amplification,
(for channels 1-6, G_2=52.5,

for channels 6 and 7, G_2=2.6),

G_3 = effective gain of the low-pass filter (1.907),

G_4 = amplification due to the PGA.

For channels 1 to 6, the voltage gain range was from 5000 (when PGA gain was 1) to 2.5 x 10^6 (when the PGA gain was 500). The CNV amplitude was generally between -4μV and -15μV, and the EOG potentials had a maximum magnitude of 1mV. As the A/D had a full-scale voltage range of $\pm$10V, sufficient gain was provided prior to the digitisation. For channels 7 and 8 the voltage gain was from 250 (when PGA gain was 1) to 125000 (when PGA gain was 500). As the ECG and the PGA magnitudes were within $\pm$3mV range, the allocated gain range for channels 6 and 7 were therefore sufficient.

3.9 The Timing Circuit

A timing circuit was required for the following reasons: i) to provide the sample and hold signal, ii) to measure the random inter-trial interval between the successive CNV trials and iii) to measure the subjects' reaction times. The block diagram of the timing circuit is shown in Figure (3.12). This circuit was based on two Intel 8253 software programmable interval timers. Each programmable interval timer contained three counters (ie. counters 0, 1 and 2) which could individually be programmed in several modes. Hall [1988] described in detail the structure and the modes of operation of the Intel 8253 device. The programmable interval timers were incorporated into the IBM PC by adding them to a vero-board which had the necessary address decoding circuits for the devices added to it. This board was placed in an expansion slot of the PC.

Figures (3.13a) and (3.13b) show the interconnections from the programmable interval timers to the various buses of the PC. The PC had a clock, the frequency of which was 6MHz. The frequency of this clock was divided by four using two

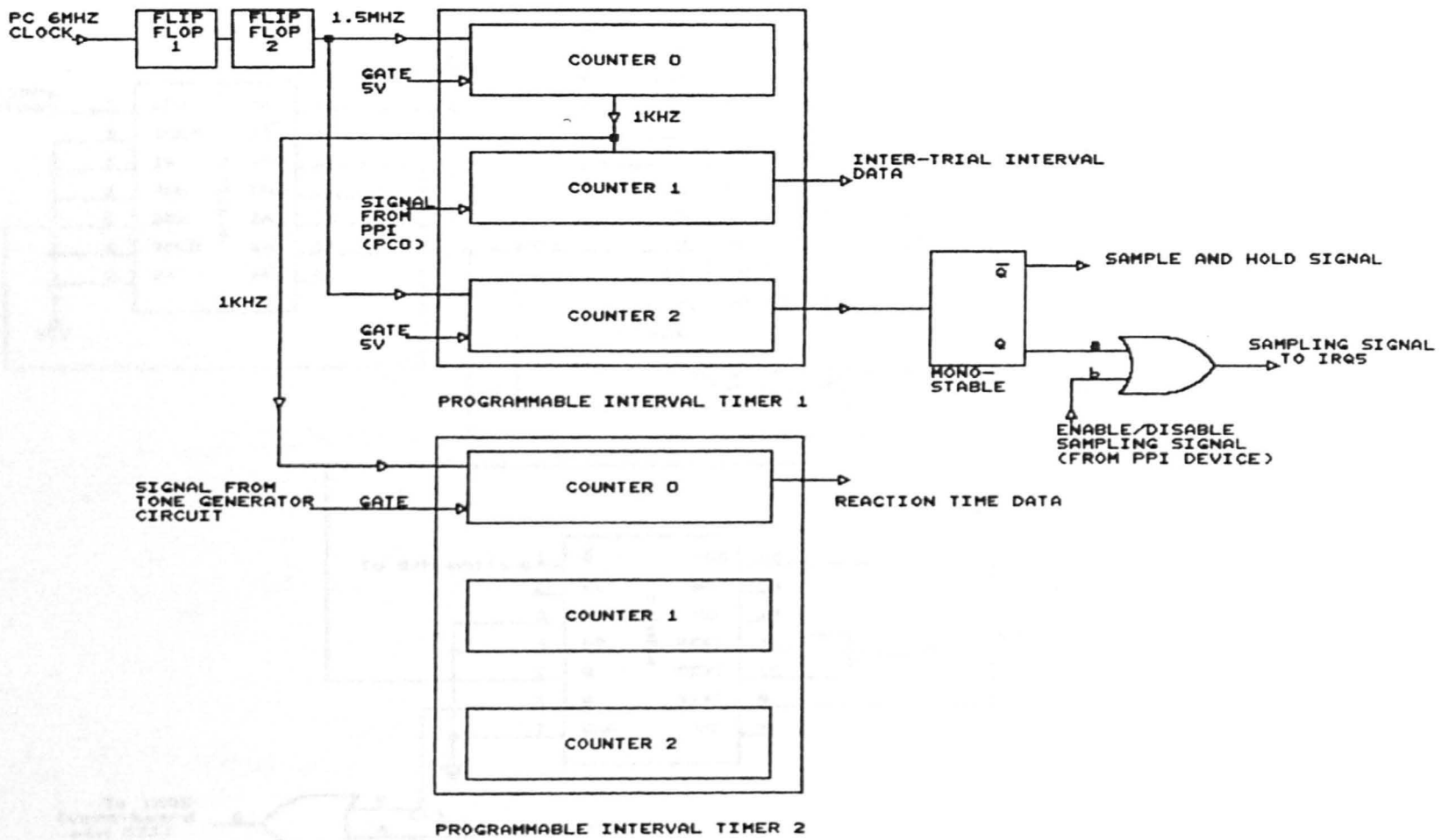


Figure 3.12 Timing circuit block diagram.

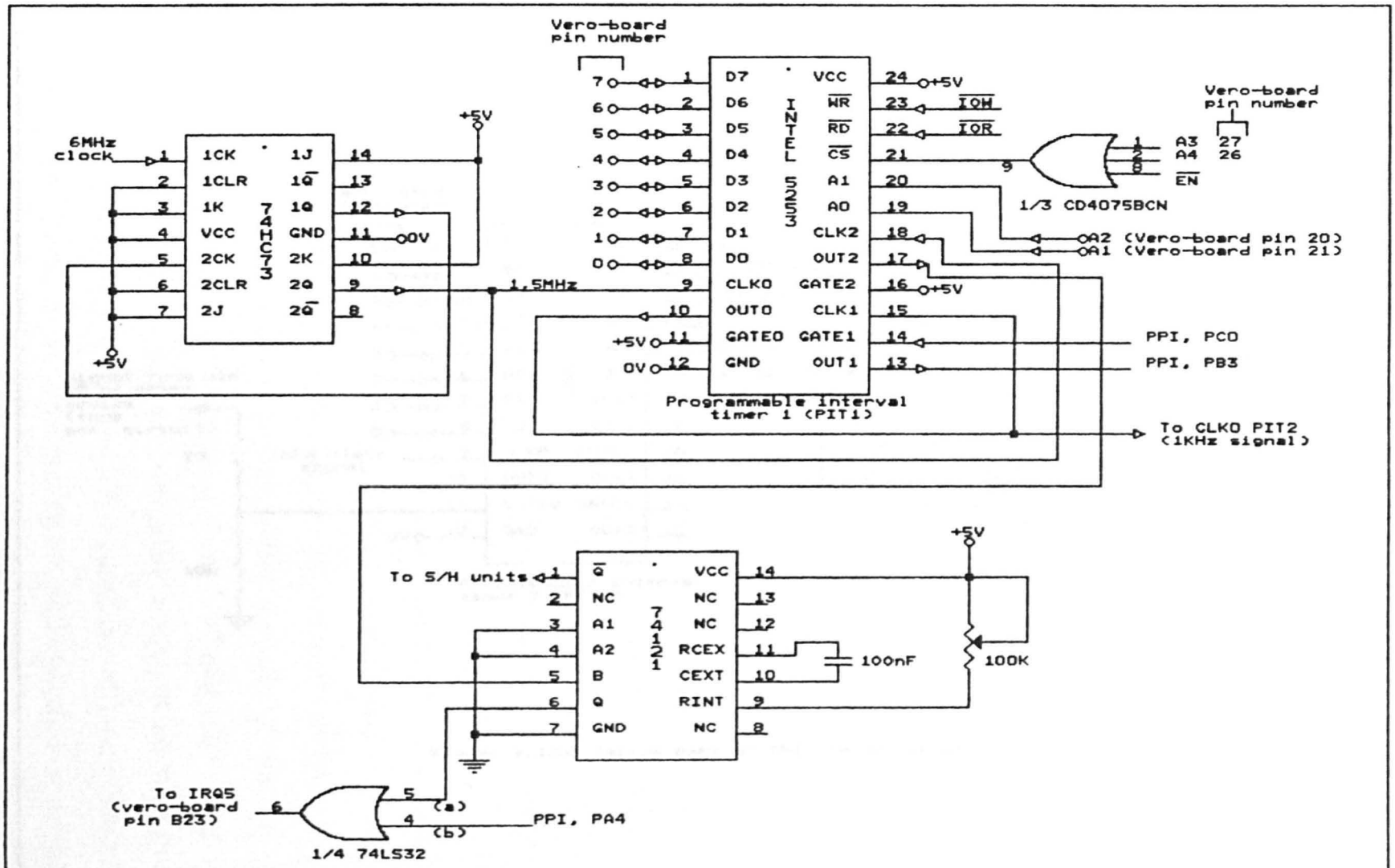


Figure 3.13a First part of the timing circuit.

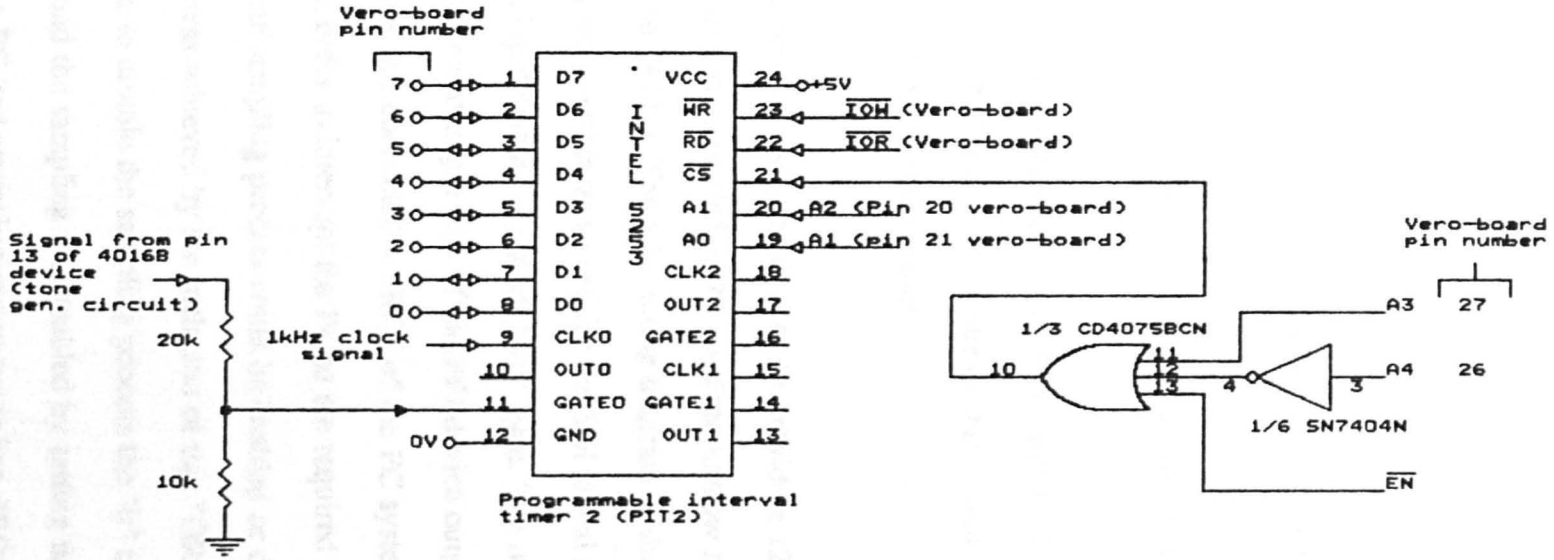


Figure 3.13b Second part of the timing circuit.

flip-flops (type 74HC73) connected together in series. The reduction in the clock frequency was necessary as the maximum permissible input clock frequency for the 8253 programmable interval timer was 2.6MHz. The resulting 1.5MHz clock signal was used as the clock signal for the counters 0 and 2 of the programmable interval timer 1. The function of each counter in the programmable interval timer 1 follows.

Counter 0 - this counter divided the 1.5MHz clock signal by 1500. The resulting 1kHz signal was used as a clock signal for counter 1 of the programmable interval timer 1 and counter 0 of the programmable interval timer 2.

Counter 1 - this counter measured the random inter-trial interval (ITI) period between successive CNV trials. The value of this period was generated in the software and was stored in this counter.

Counter 2 - this counter was programmed to provide a 125Hz square wave signal. The 125Hz signal was converted to the required narrow sampling pulse by a mono-stable (type 74121). The S/H timing diagram is shown in Figure (3.14). The $\bar{Q}$ output of this mono-stable was used for the S/H signal and its Q output was connected to an input (input "a") of an "OR" gate. The other input (input "b") of this gate was connected to pin PA4 of the PPI device output port (ie. port A). The output of the gate was connected to IRQ5 of the PC system interrupt controller 1 (type 8259A) in order to interrupt the PC at the required sampling rate. It was necessary that the sampling process could be enabled or disabled through the software. This was achieved by the inclusion of this "OR" gate in the timing circuit. In order to disable the sampling process the "b" input of this "OR" gate was set to "1" and the sampling was enabled by setting the "b" input of this "OR" gate to "0". The PC had several interrupt types but, IRQ5 was the most suitable

(a) Programmable interval timer 1, counter 2 output (OUT2) (connected to pin 5 of the mono-stable).

(b) Q output of the mono-stable (connected to OR gate "a"-input).

(c) $\overline{Q}$ output of the mono-stable to sample and hold devices.

(d) Output of the OR gate to IRQ5 (the interrupt is enabled at A in this diagram).

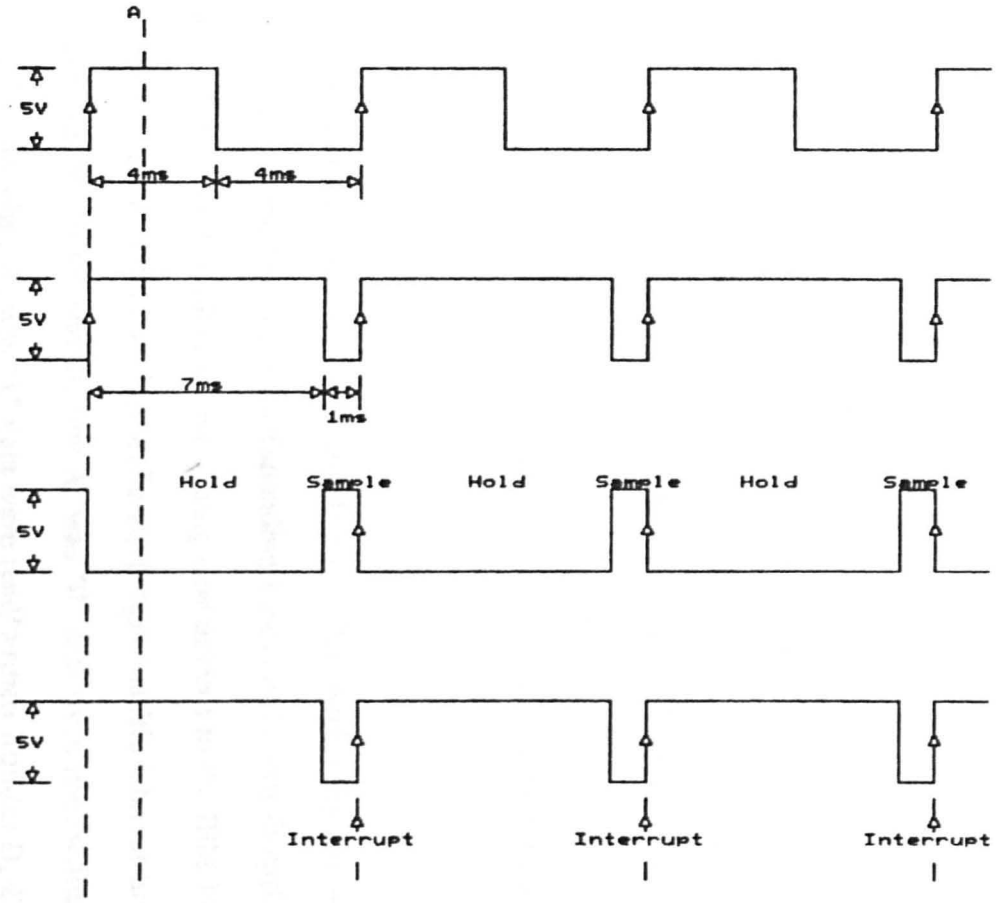


Figure 3.14 Sample and hold timing diagram.

type for this purpose (for more information refer to IBM technical reference, [1985]).

Only the counter 0 in the programmable interval timer 2 was used. This function of this counter was to measure the subjects' reaction times. A signal from the tone generator was fed to the gate of this counter. This signal started the counter at the onset of the tone and when the push-button was pressed, it stopped the counter. As the frequency of the clock input to this counter was 1kHz, the value read from it represented the reaction time in milliseconds (ie. 1/1kHz = 1ms). The other two counters in this programmable interval timer may be utilised in the future expansion of the system.

For each programmable interval timer, the data (D_0-D_7), read ($\overline{RD}$) and write ($\overline{WR}$) buses were connected to the corresponding buses on the vero-board. The base address 300 (Hex.) is allocated for adding new devices to the IBM PC system. The PC had a 16-bit data bus while the programmable interval timers had an 8-bit data bus. When the address line A_0 was "0" data were read/written from/to D_0-D_7 and when A_0 was "1" data were read/written from/to D_8-D_{15}. In this application the data lines D_0-D_7 were used, therefore whenever the timers were addressed, A_0 was "0". The address lines A_1 and A_2 from the PC were connected to the programmable interval timers address lines A_0 and A_1 respectively. The address lines A_1 and A_2 determined which counter was accessed. The control register of each programmable interval timer, which was used to program the counters, was also selected through A_0 and A_1. To select a programmable interval timer, the chip select input $\overline{cs}$ of that timer was set to "0". The chip select input for the programmable interval timer 1 was obtained from the output of a 3-input "OR" gate. The inputs to this gate were the address lines A_3 and A_4, and the enable line ($\overline{En}$) from the PC. For programmable interval timer 2, the $\overline{cs}$ input was obtained from the output of another 3-input "OR" gate. The

inputs to this "OR" gate were the address lines A_3, A_4, and the $\overline{En}$ line from the PC. The address line A_4 had to be inverted to reflect the address decoding (refer to Tables (3.2) and (3.3)).

Table (3.2) Addresses used to select the ports in the programmable interval timer 1.

Address Lines					Address in (Hex.)	Port Selected
A4	A3	A2	A1	A0		
0	0	0	0	0	300	counter 0
0	0	0	1	0	302	counter 1
0	0	1	0	0	304	counter 2
0	0	1	1	0	306	control register

Table (3.3) Addresses used to select the ports in the programmable interval timer 2.

Address Lines					Address in (Hex.)	Port Selected
A4	A3	A2	A1	A0		
1	0	0	0	0	310	counter 0
1	0	0	1	0	312	counter 1
1	0	1	0	0	314	counter 2
1	0	1	1	0	316	control register

3.10 Acoustic Stimuli Generator

To elicit the CNV it was necessary to present a warning and an imperative stimulus to the subjects. Some investigators such as Tecce [1972] used a light flash for the warning stimulus and a tone for the imperative stimulus. It was decided to use a click and a tone for the warning and imperative stimuli respectively. The light flash was not used for the warning stimulus as it can cause blinking. This in turn results in ocular artefact.

3.10.1 Click Generator

The click generator circuit is shown in Figure (3.15). The base of a transistor (this transistor performed as a digital switch) was connected to pin PA6 of the PPI device port A and its collector was connected to the input of a mono-stable multi-vibrator (type HEF4528B). On the rising edge of a pulse sent to the base of this transistor, the mono-stable generated a narrow pulse (the width of which was set by the values of R and C). The output of the mono-stable was connected to the enable input (E_1) of an analogue switch (type HEF4016B). The input terminal of the switch (Y_1) was connected to the centre pin of a 500kΩ potentiometer and the output of the analogue switch (Z_1) was connected to a power amplifier (the power amplifier is described in section (3.10.3)). During the short period that the mono-stable output was high (ie. logic "1"), a d.c. voltage was transmitted through the analogue switch to the power amplifier. This produced a click. The intensity of the click was adjusted by using a 500kΩ potentiometer.

3.10.2 Tone Generator

The tone generator circuit is shown in Figure (3.16). The base of a transistor (this transistor was used as a digital switch) was connected to pin PA7 of the PPI device port A and its collector to the input (Iob) of a mono-stable multi-vibrator (type HFE4528B). The mono-stable circuit produced a square pulse (the duration of the pulse was set to 6 seconds) on the rising edge of a pulse sent through the PPI device to the base of the transistor. The output of the mono-stable was connected to the enable input (E_0) of an analogue switch (type HEF4016B). During the period that the output of the mono-stable was logic "1" a waveform (frequency= 1kHz), produced by a circuit based on a 555N device, was transmitted to the power amplifier through the analogue switch. This produced a tone. The intensity of the tone was adjusted using a 500kΩ potentiometer.

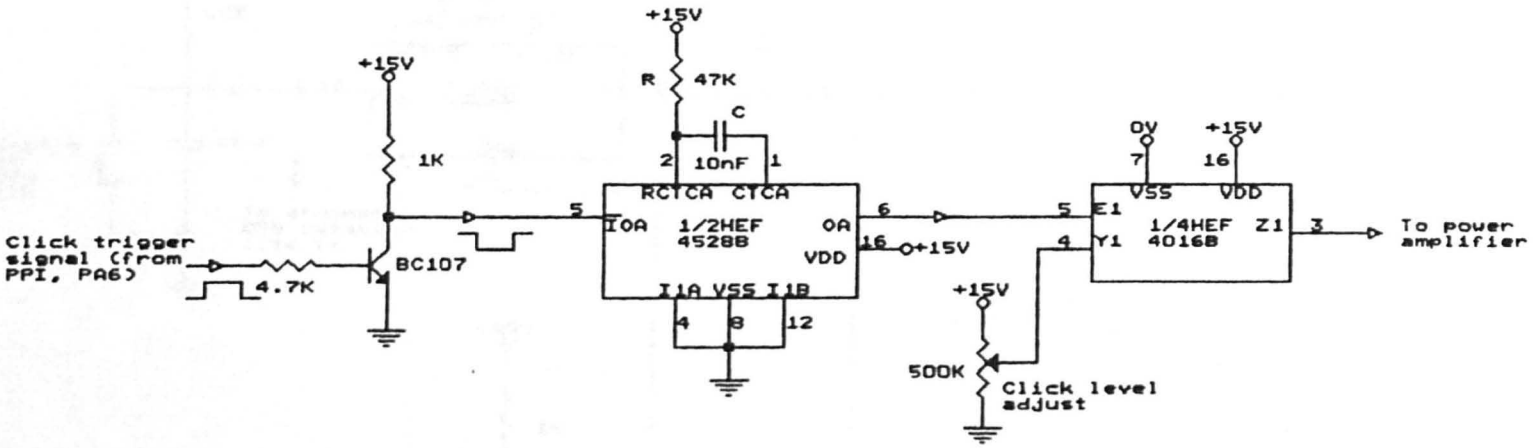


Figure 3.15 Click generator circuit.

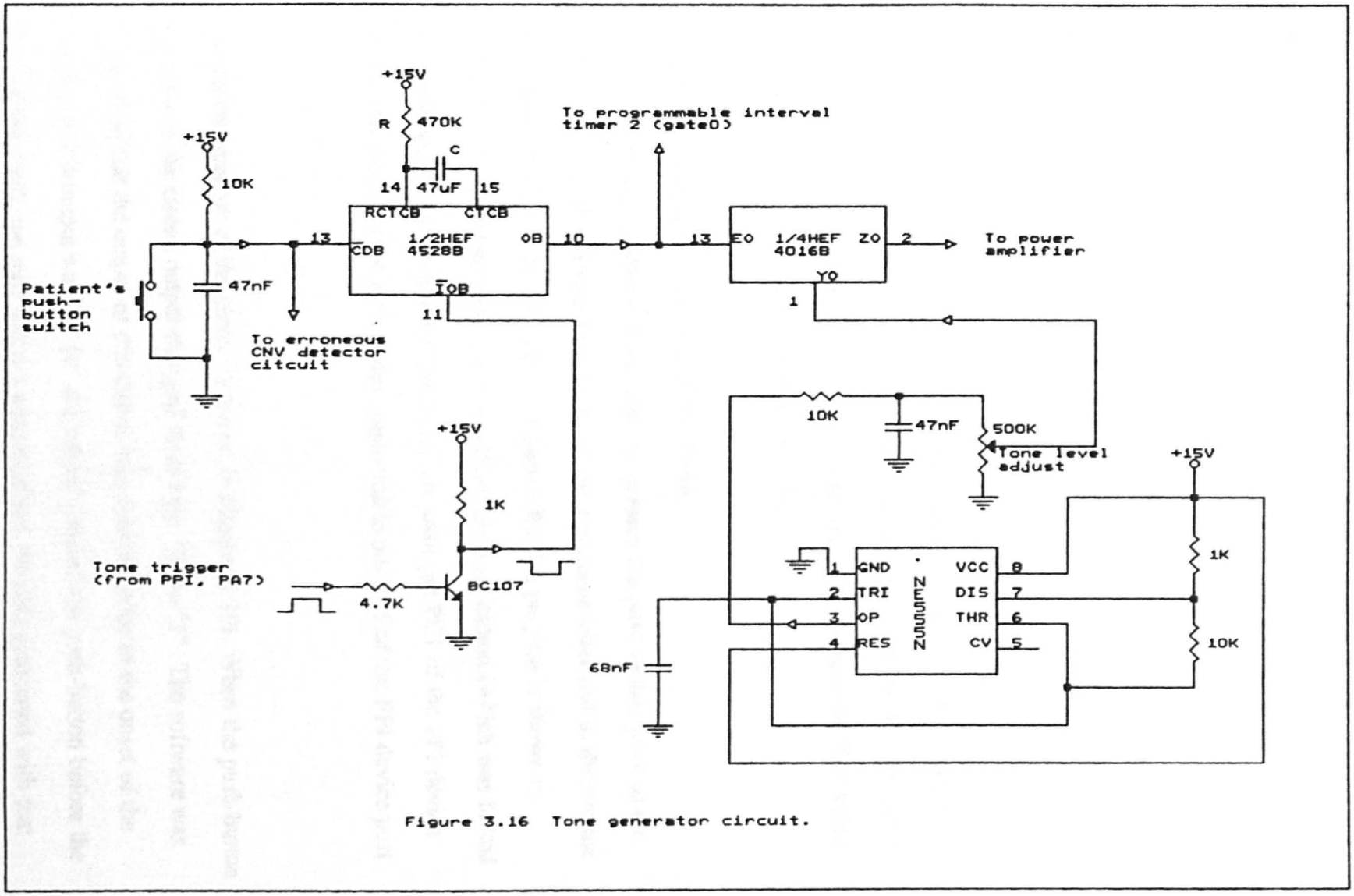


Figure 3.16 Tone generator circuit.

A wire linked a push-button to the clear direct input ($\overline{C}DB$) of the mono-stable. The subjects, by pressing the push-button, cleared the output of the mono-stable, thus terminating the tone.

The output of the mono-stable (O_B) was also connected to the gate of counter 0 in the programmable interval timer 2 (see section 3.9) in order to measure the subjects' reaction times.

3.10.3 Audio Power Amplifier

A circuit based on the TBA820 device provided the necessary power amplification of the click and the tone signals. This circuit was obtained from the RS data sheet [1985]. The output of this circuit was connected to an 8Ω loudspeaker. The audio power amplifier circuit is shown in Figure (3.17).

3.11 Circuit to Detect Erroneous CNV Trials

The CNV trial was erroneous if the subjects pressed the push-button prior to the onset of the tone. It was necessary to detect the erroneous trials and to discard the data associated with them. The circuit designed for this purpose is shown in Figure (3.18). It had two inputs, one was from the push-button (which was linked to the tone generator circuit) and the other was from pin PC1 of the PPI device port C. The output of the circuit was connected to pin PB5 of the PPI device port B.

The timing diagram of the circuit is shown in Figure (3.19). When the push-button was pressed the circuit output changed from logic "0" to "1". The software was designed so that the output of this circuit was checked prior to the onset of the tone and if this output was "1" (ie. the subject pressed the push-button before the onset of the tone), the tone was not generated and the data associated with that trial were discarded. The output of the circuit was cleared by the software to "0"

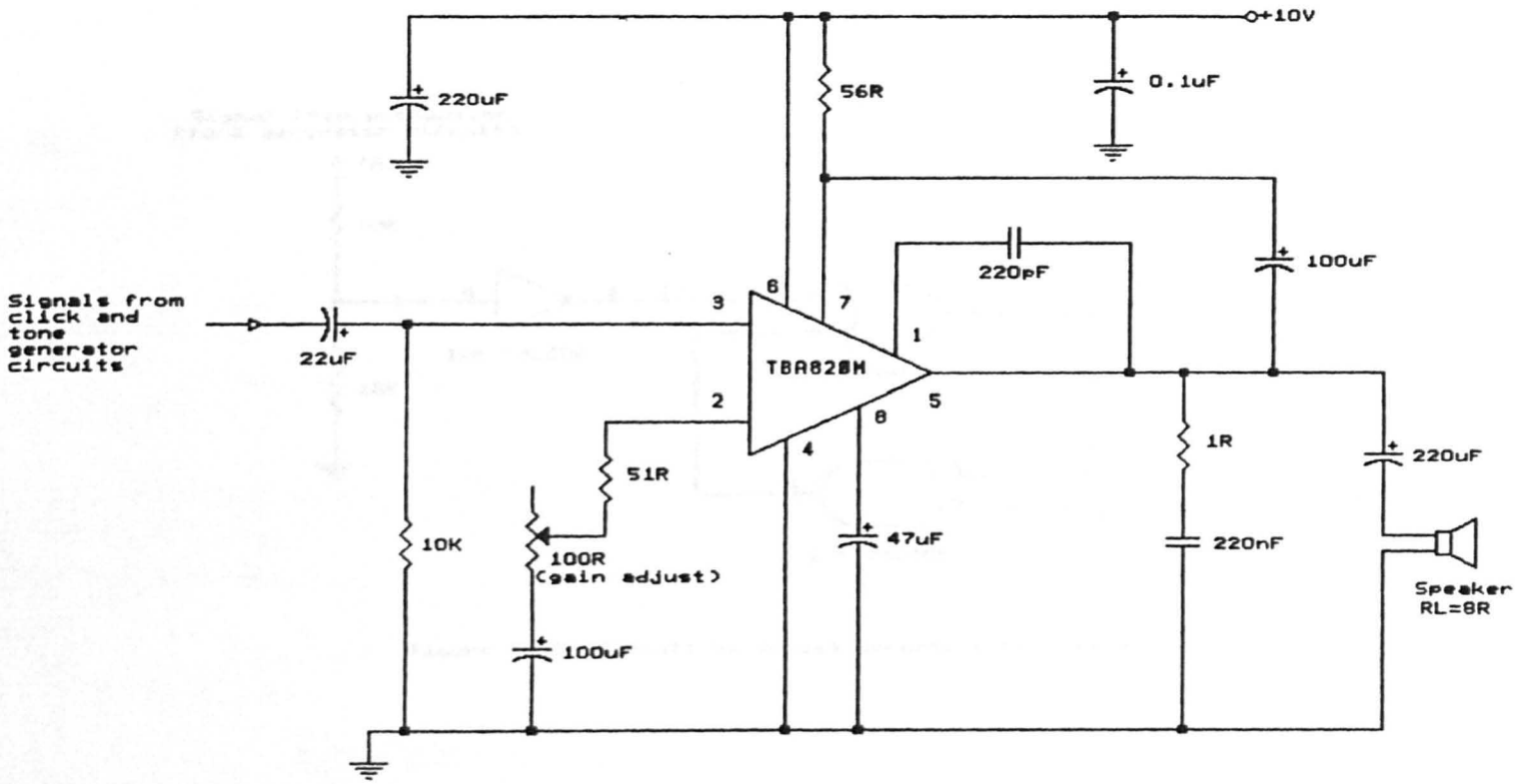


Figure 3.17 Audio power amplifier circuit.

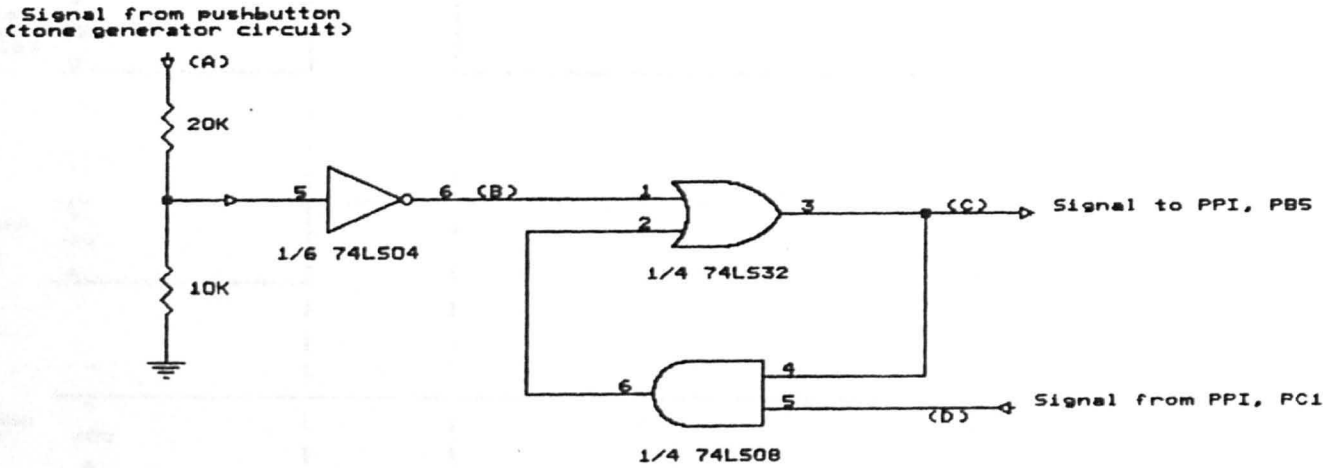


Figure 3.18 Circuit to detect erroneous CNV responses.

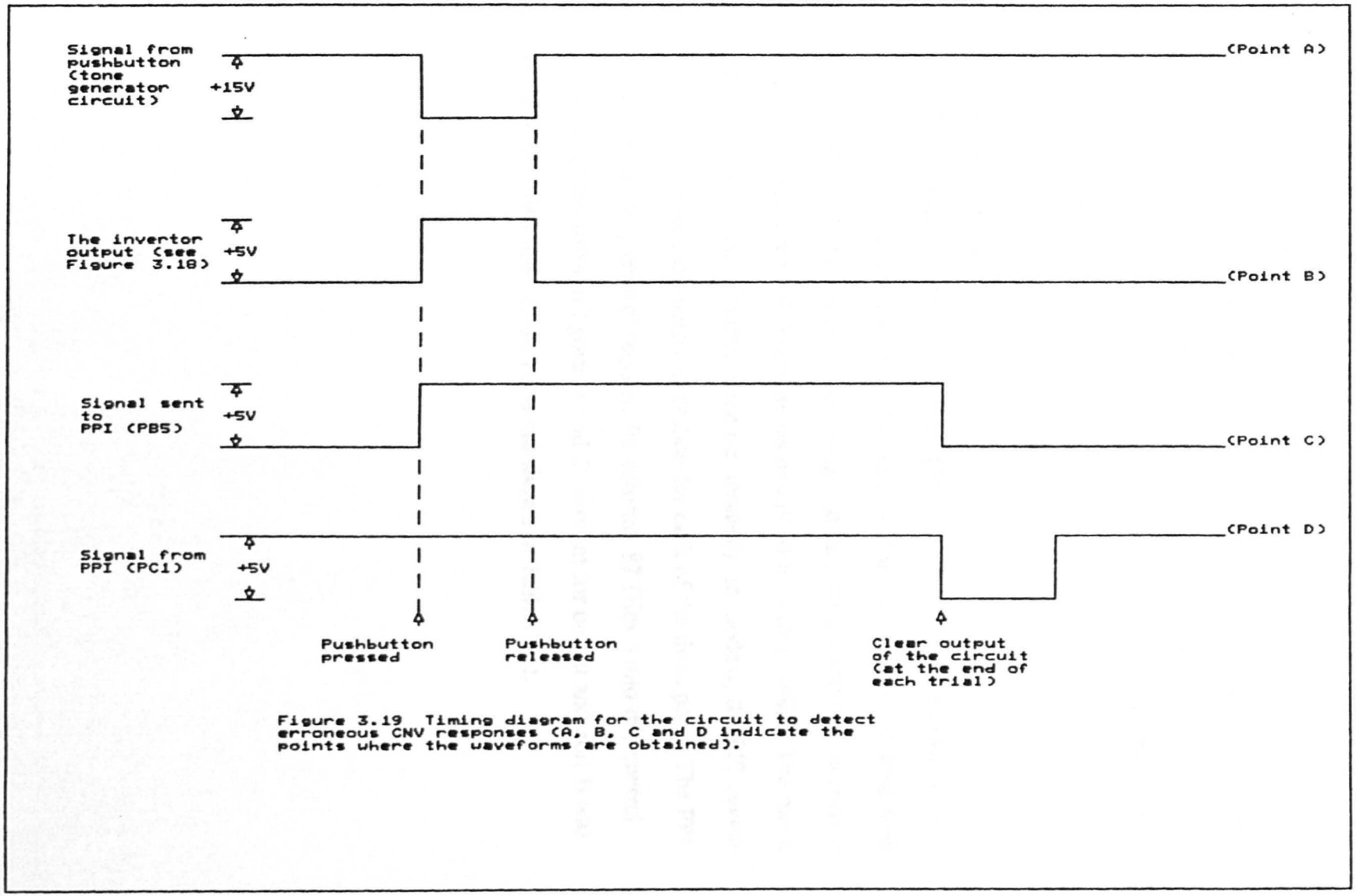


Figure 3.19 Timing diagram for the circuit to detect erroneous CNV responses (A, B, C and D indicate the points where the waveforms are obtained).

through pin PC1 of the PPI device port C at the end of each CNV trial recording.

3.12 Operator Switch and System LED

An operator switch was incorporated (as shown in Figure (3.20)) so that if it .pn 101 became necessary the operator could provide a pause in the data recording. An LED was included to indicate when the data recording was in progress. Figure (3.21) shows its circuit diagram.

3.13 Digital Interfacing

An Intel programmable peripheral interface (PPI) device (type 8255A) was used for the interfacing of the devices to the PC system. The PPI device had three 8-bit ports (A, B and C). The ports could be configured through the software in several modes to perform a variety of functions (as described by Hall [1988]). The mode selected was the basic input/output mode (ie. mode 0). In mode 0, the PPI device provided a simple input and output operation for each of the three ports. The PPI device had a write only control register. By entering 82 (Hex.) into this control register (through the software) ports A and C were set for output and port B was set for input. The functions of the ports are shown in Table (3.4).

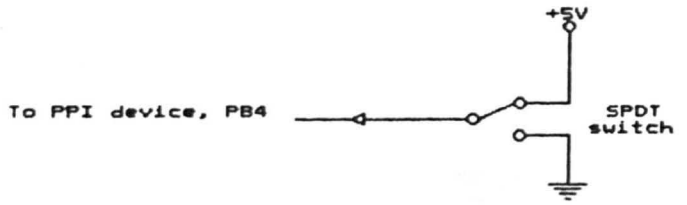


Figure 3.20 Operator switch circuit.

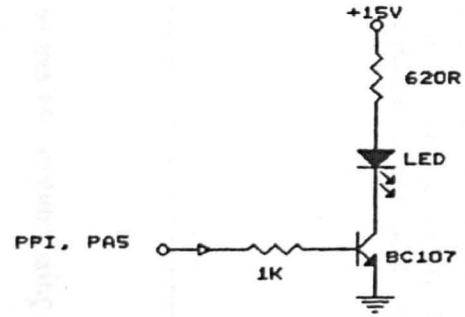


Figure 3.21 Instrumentation system LED circuit.

Table (3.4) Functions of the ports in the PPI device.

Port	Bit	Function
A	0	multiplexer channel select
	1	
	2	
	3	
	4	enable/disable sampling
	5	LED command
	6	click generator trigger
	7	tone generator trigger
B	0	window detector output
	1	
	2	
	3	programmable interval timer 1 counter 1 output
	4	operator switch output
	5	CNV error detector circuit clear command
	6	not used
	7	
C	0	programmable interval timer 1 counter 1 gate
	1	CNV error detector circuit output
	2	not used
	3	
	4	
	5	
	6	
	7	

The PPI device was added to the PC system using the vero-board (described in section 3.9). Figure (3.22) shows the method of connecting the PPI device to the vero-board. The device data pins (D_0-D_7) were connected to the system data bus (D_0-D_7). The read ($\overline{RD}$) and write ($\overline{WR}$) pins were connected to the corresponding lines ($\overline{IOR}$ and $\overline{IOW}$) of the vero-board. The ports A, B and C and the control register were selected using the address lines A_0 and A_1. The A_0 and A_1 pins were connected to the vero-board lines A_1 and A_2 respectively. The PPI device was selected when the chip select pin ($\overline{CS}$) was low. This was achieved using a circuit shown in Figure (3.23). The addresses used for selecting the ports and the control register are shown in Table (3.5).

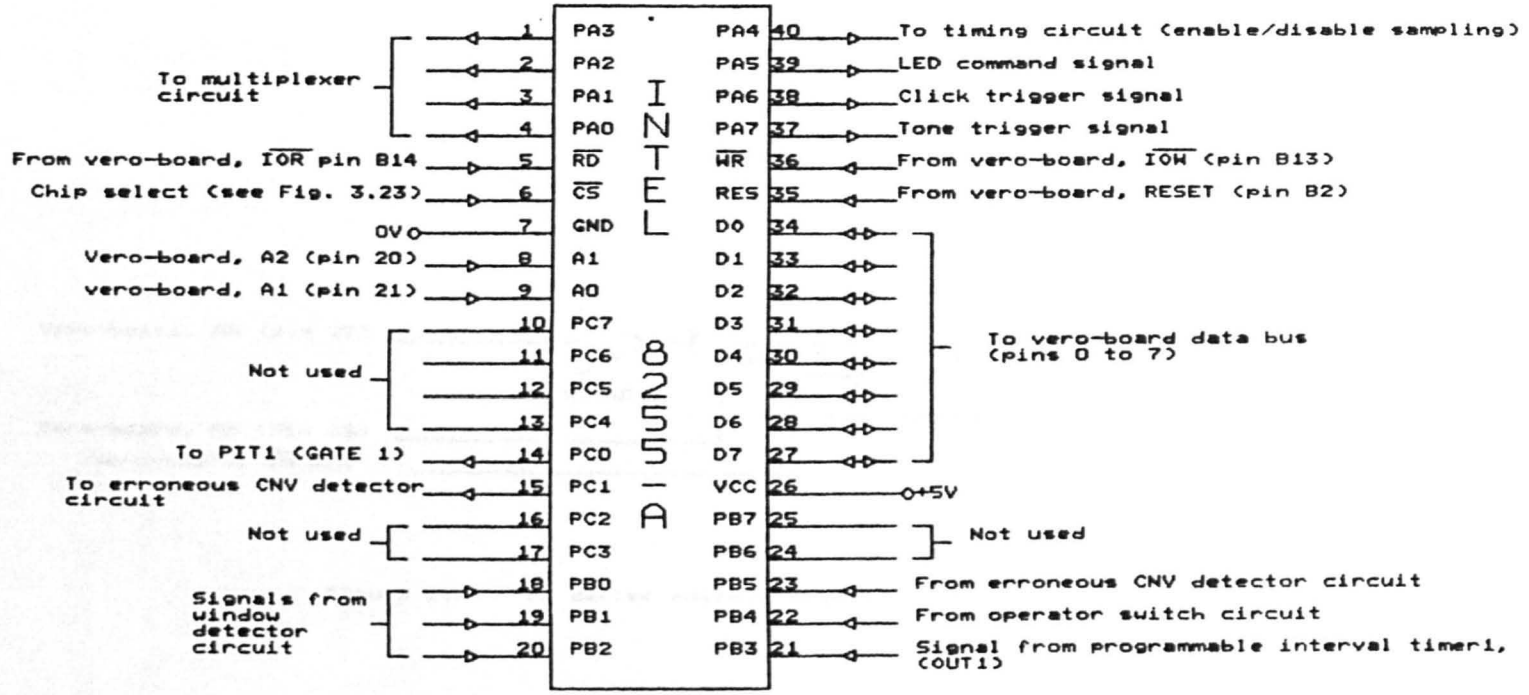


Figure 3.22 Interconnection between the PPI device and vero-board.

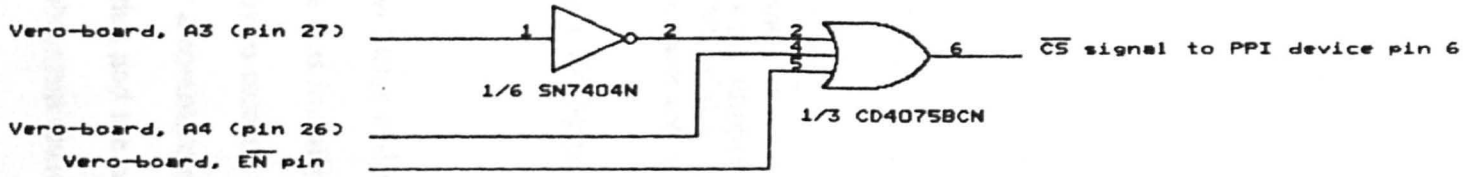


Figure 3.23 PPI device address decoder.

Table (3.5) Addresses used to select the PPI ports.

Address Lines					Address in (Hex.)	Port Selected
A4	A3	A2	A1	A0		
0	1	0	0	0	308	port A
0	1	0	1	0	30A	port B
0	1	1	0	0	30C	port C
0	1	1	1	0	30E	control register

3.14 Data Storage Requirement

The number of bytes (N_b) for a recording containing 32 trials was calculated using,

$$N_b = S_r \times N_c \times B_s \times T \times N_t \qquad ...(3.10)$$

where S_r was the sample rate = 125Hz,
N_c was the number of channels = 8 channels,
B_s was the number of bytes per sample = 3 bytes,
T was the duration of a CNV trial = 12 seconds,
and N_t was the number of trials recorded = 32 trials.

Using (3.10), N_b was equal to 1.152×10^6 bytes (ie. 125 x 8 x 3 x 12 x 32).

3.15 Data Storage Facility

The recorded data related to the waveforms and the reaction time values for each subject were kept in a file. This file was initially stored on the hard disk of the PC and then copied into a 20 megabytes cassette using a Sysgen tape streamer. This data transfer was controlled by a commercially available program called FBACK. A description of this program and the procedure for the data transfer is provided in Sysgen Smart Image Subsystem Owner's Manual [1985].

3.16 Hardware Testing

Initially the sections of the hardware were separately tested to ensure they functioned in accordance with the specifications. The gain and d.c. offset of each

amplifier and the phase and frequency responses of the filters were monitored. Signals with different amplitudes were applied to the WD and the output of the WD was examined. Tests were carried out to ensure the counters in the 8253 programmable interval timers functioned as described in section 3.9. This included observing the 125Hz square wave signal generated by the counter 2 (in the programmable interval timer 1) on the oscilloscope. The timing diagram of the interrupt signal (shown in Figure (3.14)) was observed on the oscilloscope and it was ensured it had a correct relationship with the sample and hold signal. The PPI device was tested through software by reading and writing digital test data to and from its ports. The operation of the stimuli generator unit was checked. The circuit responsible for detecting erroneous CNV trials was tested by pressing the push-button prior the onset of the tone. The device correctly detected the faulty CNV trials.

The phase and frequency responses of the system up to the S/H units were obtained using a frequency analyser. The set-up used is shown in Figure (3.24). The phase and frequency responses obtained for channel 1 are shown in Figures (3.25) and (3.26) respectively. The operation of the DT2805 was tested by applying a calibration signal to the board, digitising the signal, storing the digitised data on the hard disk and then plotting the stored data. The operation of the complete recording system was tested by applying a calibration signal to the EEG machine head-box and recording the signals using the eight channels. This indicated that the system correctly recorded and stored the data on the hard disk.

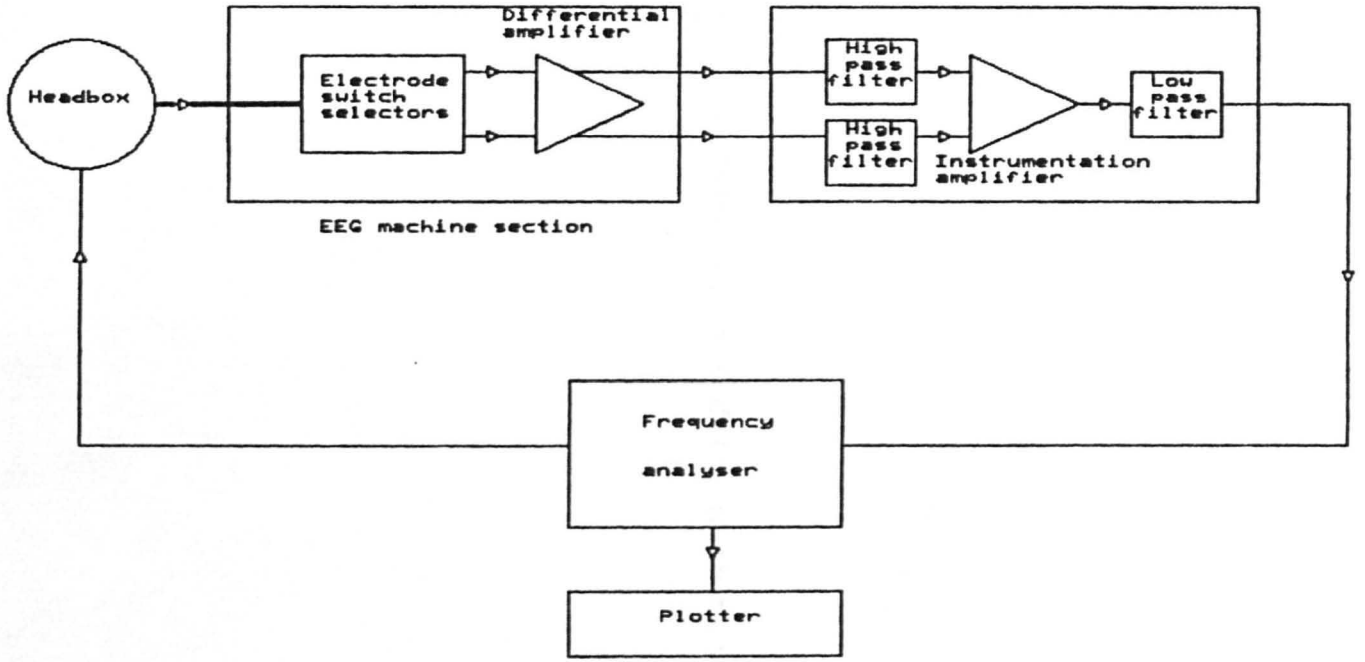


Figure 3.24 Set-up used to obtain the phase and frequency responses.

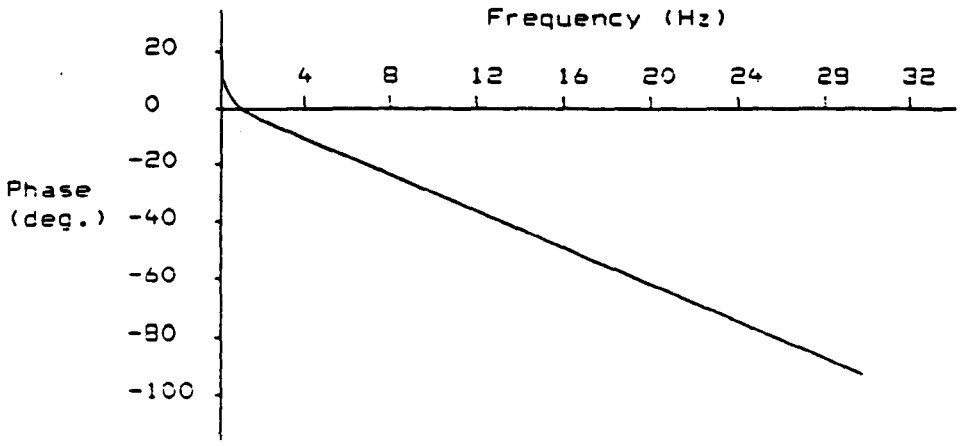


Figure 3.25 Phase response of the instrumentation system.

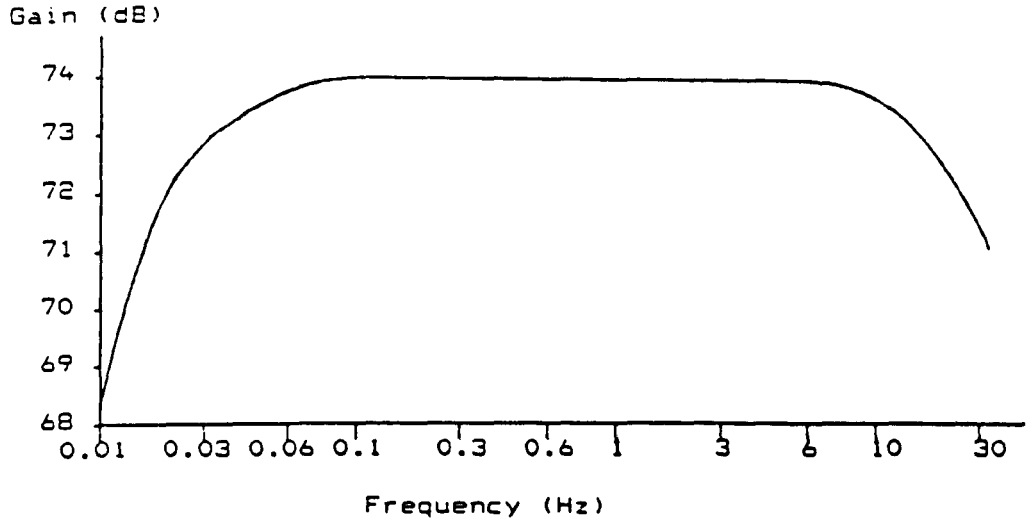


Figure 3.26 Frequency response of the instrumentation system.

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Chapter 4 Description of the Data Recording Software

The data recording software had two main sections. The first section was written in the Turbo Pascal programming language and it was called "ACQ.PAS". The second section was written in assembly language (Intel 80286) and was linked to the Pascal program. The assembly language program was called "SAMPLE1.ASM". The listing of the data recording software is provided in Appendix (A).

4.1 Description of the Pascal Program Section

This section initialised and tested the DT2805 board (this board was used for its programmable gain amplifier (PGA) and analogue to digital converter (A/D)) and it acquired the following data recording information from the operator:

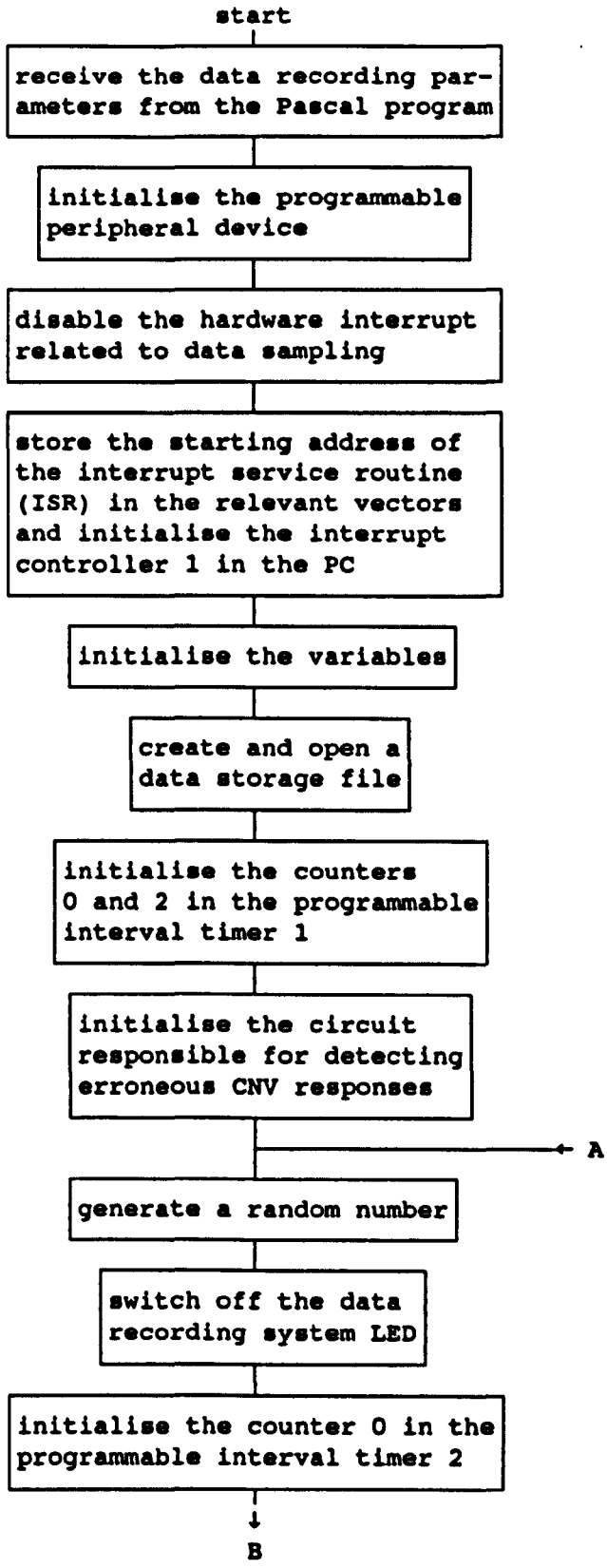
- The pre-warning-stimulus record length (in seconds).
- The inter-stimulus interval duration (in seconds).
- The post-imperative-stimulus record length (in seconds).
- The number of CNV trials to be recorded.
- A filename for data storage.

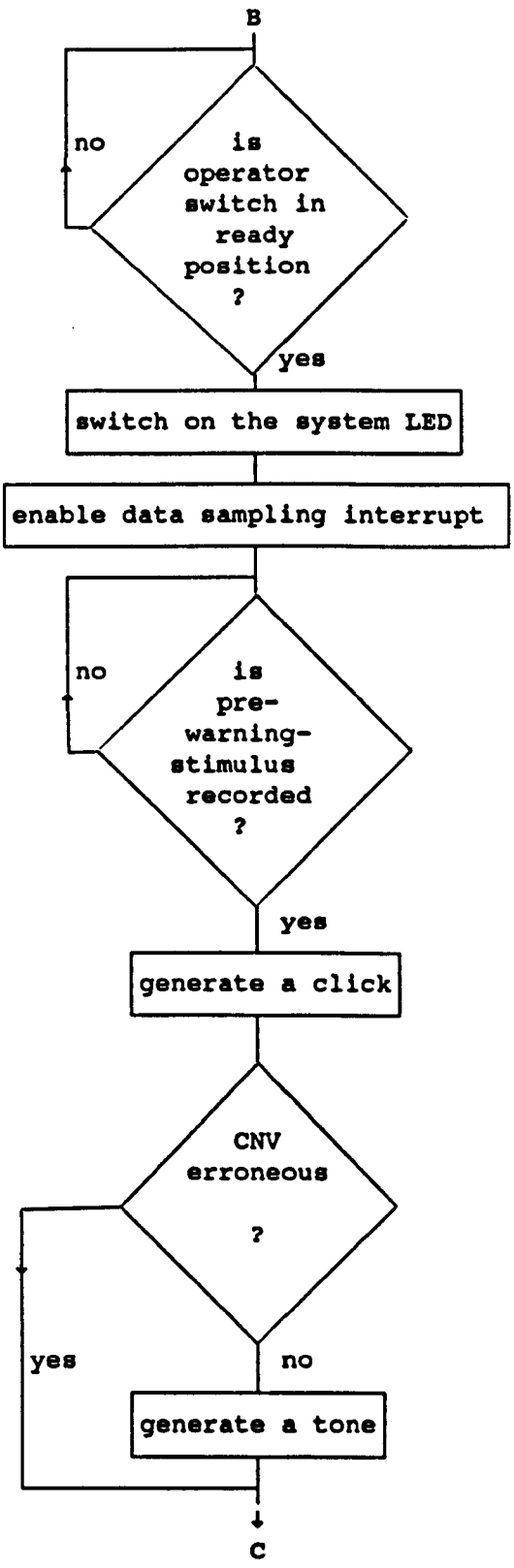
It then requested the operator to select an option. The options were familiarisation, practice and data recording. The purpose of familiarisation option was to ensure that the subjects could recognise the warning and imperative stimuli. When this option was selected a series of 10 click and tone pairs were generated by the instrumentation system and the subjects listened to the sounds. The practice option was for ensuring that the subjects were able to respond correctly to the imperative-stimulus. Selection of this option produced 15 click and tone pairs. The subjects terminated the tones by pressing a push-button. Selection of the data recording option initiated the recording of data.

When the operator selected one of the above options, the Pascal program called the assembly language program and the requested option was performed. After the completion of data recording, the ACQ Turbo Pascal program displayed the data (sample values) for recorded waveforms, values of the reaction times associated with the CNV trials and the averaged value of the reaction time.

4.2.1 Description of the Assembly Language Section

This section received the durations of the pre-warning-stimulus record length, inter-stimulus interval, post-imperative-stimulus record length and the number of CNV trials from the Pascal program. It then followed the steps necessary for execution of the chosen option. The same assembly language program was used for familiarisation, practice and data recording options (files created after performing the familiarisation and practice options were automatically discarded). A flow chart illustrating the operation of the assembly language program is shown in Figure (4.1).


start
receive the data recording parameters from the Pascal program
initialise the programmable peripheral device
disable the hardware interrupt related to data sampling
store the starting address of the interrupt service routine (ISR) in the relevant vectors and initialise the interrupt controller 1 in the PC
initialise the variables
create and open a data storage file
initialise the counters 0 and 2 in the programmable interval timer 1
initialise the circuit responsible for detecting erroneous CNV responses
A
generate a random number
switch off the data recording system LED
initialise the counter 0 in the programmable interval timer 2
B


B
no
is operator switch in ready position ?
yes
switch on the system LED
enable data sampling interrupt
no
is pre-warning-stimulus recorded ?
yes
generate a click
CNV erroneous ?
yes
no
generate a tone
C

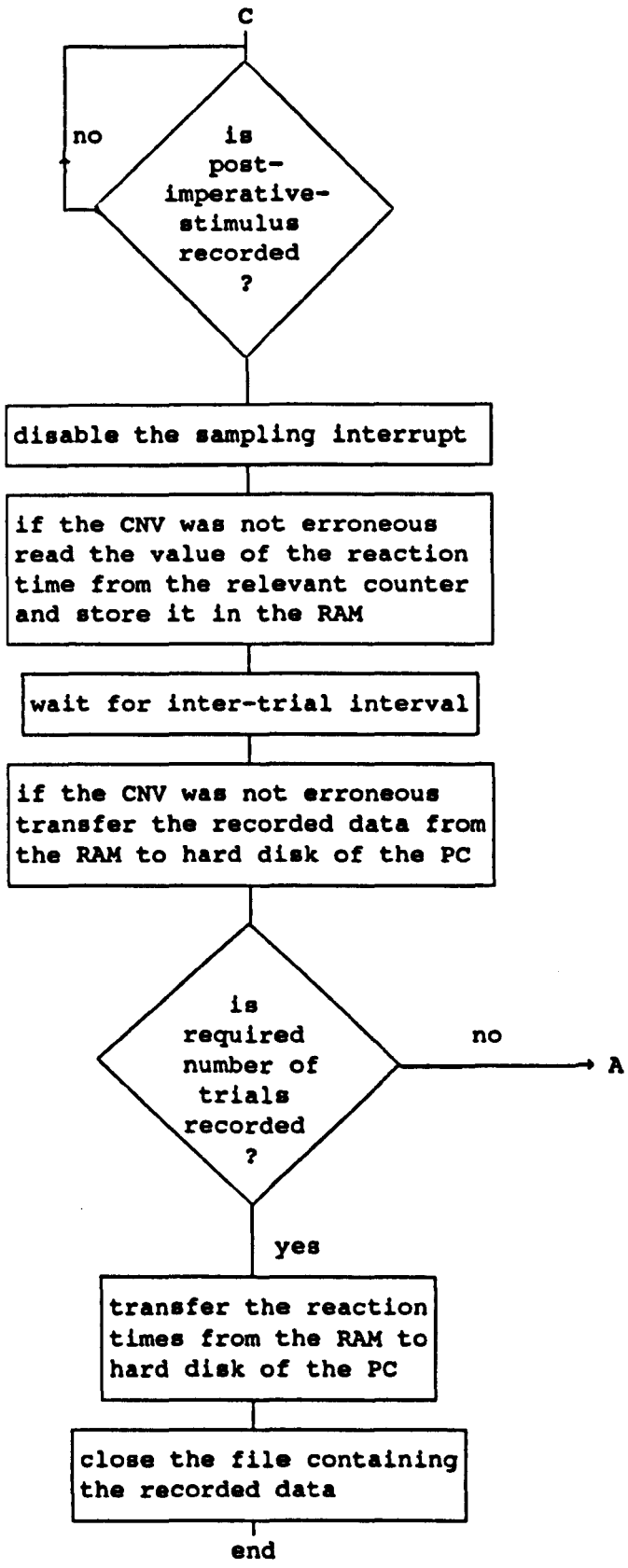


Figure (4.1) Flow chart describing the operations of the assembly language program.

Before describing the operations carried out in the assembly language program it would be advantageous to briefly introduce a process known as "disk operating system (DOS) function call" [Disk operating system, 1985]. This process was used several times in the assembly language program to perform operations such as creating a file, opening a file, closing a file and transferring data from the random access memory (RAM) to the hard disk of the PC. DOS provides a wide variety of functions which can be accessed in assembly language program through the DOS function calls. This enables options such as character input/output, file management and memory management to be carried out. In order to perform a DOS function call specific registers and pointers must be initialised as described in DOS technical reference manual [1985]. The interrupt type 21 (Hex) is then issued. This causes the requested task to be performed.

The operations performed in the assembly language program were as follows.

1) The programmable peripheral interface (PPI, Intel 8255A-5) device was initialised so that it provided two 8-bit digital output ports (ie. ports A and C) for writing digital data to external devices and an 8-bit input port (ie. port B) for reading digital data from external devices. The PPI device initialisation was achieved by writing 82 (Hex.) into its control register as described by Hall [1988].

2) The hardware interrupt related to data sampling was disabled by setting the enable/disable sampling signal high (see Figure (3.12)).

3) The starting address of the interrupt service routine (ISR) was stored in the relevant vectors (ie. 34 (Hex.) and 36 (Hex.)). These vectors were associated with the hardware interrupt request 5 (IRQ5). IRQ5 was selected after referring to the IBM technical reference manual [1985]. The instructions contained in the ISR were executed following an interrupt request. During the execution of the ISR,

signals from the 8 channels were sampled, digitised and stored in random access memory (RAM) of the PC. A variable (called SAMPNO) which contained the total number of samples obtained during the recording of the trial was also incremented by one. The ISR function is described in detail in section 4.2.2.

4) The variables used in the assembly language program were initialised.

5) A file was created and opened on hard disk of the PC. This file was used for storing data.

6) The counters 0 and 2 in the programmable interval timer 1 were initialised. The counter 0 divided the frequency of its 1.5MHz clock signal by 1500, thus producing a 1kHz signal at its output. The counter 2 divided the frequency of its 1.5MHz clock signal by 12000, thus producing a 125Hz signal at its output. The 125Hz signal was used in the S/H circuit and it also provided the necessary hardware interrupt to the main microprocessor of the PC.

The operations (1)-(6) were performed only once during data recording. The following steps were repeated for every trial.

7) The circuit responsible for detecting erroneous CNV trials (see chapter (3)) was initialised by sending the necessary pulse to its initialisation input line through the PPI device port C (pin PC1). This caused the output of this circuit to be cleared to "0".

8) A random number was generated. This number was required as successive CNV trials were separated by a random period called the inter-trial interval. The value of this number was between 100 and 400 and was stored in the counter 1 of

the programmable interval timer 1.

9) The LED of the data recording system was switched off. This was achieved by setting pin PA5 in the PPI device port A low.

10) The counter 0 in the programmable interval timer 2 was initialised to measure reaction times. This was achieved by loading this counter with FFFF (Hex.) and storing 30 (Hex.) in the control register of the programmable interval timer 2. At the onset of the tone, the gate of the counter 0 was set to "1" by the tone generator circuit. This caused the initial value of this counter (ie. FFFF (Hex.)) to be repeatedly reduced by one at a rate equal to its clock input (ie. 1kHz). This continued until the push-button (which was attached to the tone circuit) was pressed, terminating the tone and stopping the counter. The value read from this counter indicated the reaction time.

11) The operator switch circuit (referred to in chapter (3)) was checked through PPI device port B (PB4) and if its output was "0", the data recording was halted until the operator set the output of this circuit to "1" by using the switch.

12) The instrumentation system LED was switched on to indicate the system was ready for data recording. This was achieved by setting the input to the LED circuit to "1" through PPI device port A (PA5).

13) The hardware interrupt responsible for data sampling was enabled by setting the enable/disable line of its circuit (see Figure (3.12)) to "0" through the PPI device port A (PA4).

14) The variable SAMPNO was continuously monitored. Every 8ms the instructions in the ISR were executed and the value held in the variable SAMPNO

was incremented by one. Once SAMPNO reached a pre-defined sample number for the pre-warning-stimulus interval the operation proceeded to the next section.

15) The click generator circuit was triggered to produce a click. This was performed by sending the necessary pulse to the click generator circuit through PPI device port A (PA6).

16) The value of the SAMPNO was monitored to determine how many samples were recorded. This was repeated until the recording of the inter-stimulus interval was complete.

17) The output of the circuit responsible for detecting erroneous CNV responses (refer to chapter (3)) was read. A "1" at the output of this circuit indicated the individual pressed the push-button prematurely, causing the CNV to be erroneous. If the output of this circuit was "1", the next operation (ie. generation of a tone) was skipped.

18) If the CNV was not erroneous a tone was generated by sending a pulse through PPI device port A (PA7) to the tone generator circuit.

19) The variable SAMPNO was continuously monitored until recording of the post-imperative-stimulus section was complete.

20) The enable/disable sampling signal (see Figure (3.12)) was set to "1". This disabled the sampling interrupt.

21) The value of reaction time was read from the counter 0 of the programmable interval timer 2 and if the CNV was not erroneous this value was stored in the

RAM.

22) The counter 1 of the programmable interval timer 1 was loaded with the value of random number (generated previously) and it was initialised to time the inter-trial interval. Then the gate of this counter was set to "1" through PPI device port C (PC0). This caused this counter to start counting. The output of this counter was continuously monitored through the PPI device port B (PB3). A high level ("1") at the output of this counter indicated the end of the inter-trial interval. As the frequency of the clock to this counter was 1kHz, if this counter was loaded with a value N, it took N milliseconds for its output to change to "1".

23) If the CNV was not erroneous, the recorded data were transferred from RAM to the hard disk of the PC.

24) The number of CNV trials recorded was examined. If the required number of trials was not recorded, the operations (7)-(23) were repeated.

25) The reaction time values were transferred from RAM to hard disk.

26) The CNV file containing the data was closed and control was returned to the Pascal program.

4.2.2 Description of the Interrupt Service Routine

This routine was part of the assembly language program. Its flow chart is shown in Figure (4.2).

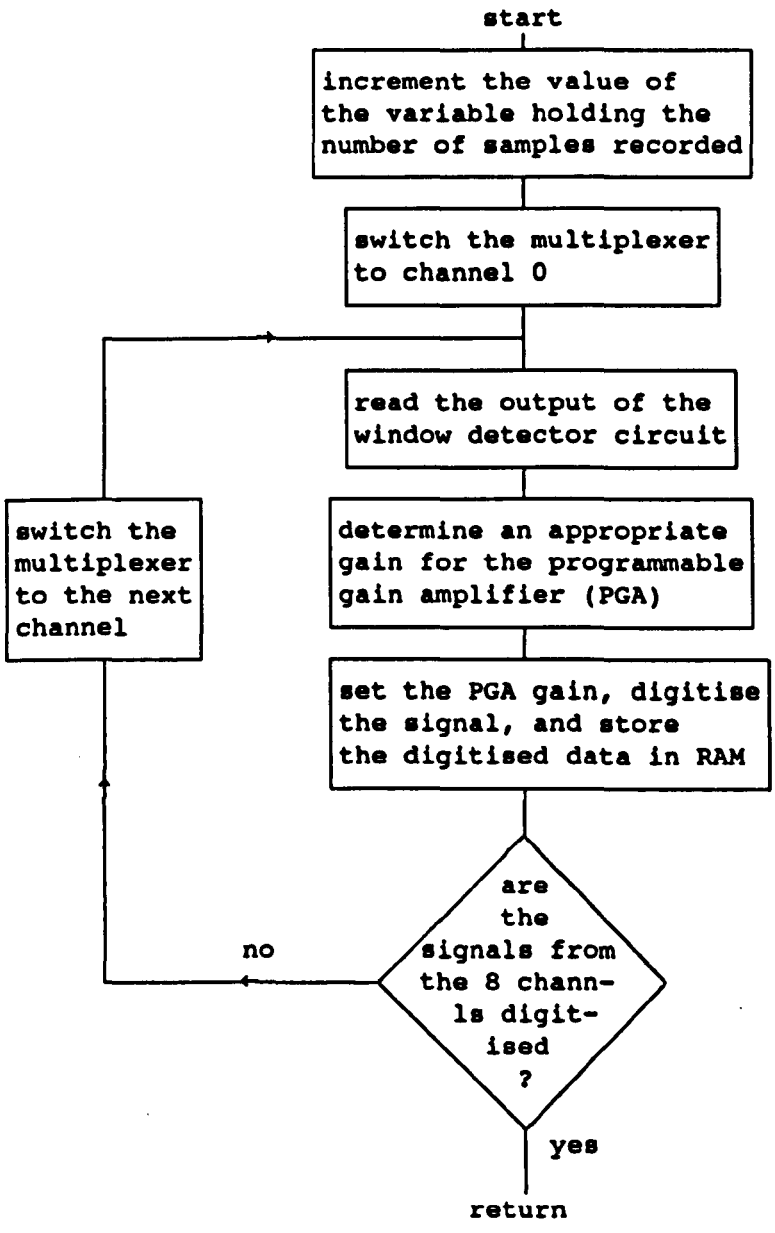


Figure (4.2) Flow chart describing the operations of the interrupt service routine.

A description of the operations performed during the execution of the ISR follows.

1) The value of the variable SAMPNO was incremented by one.

2) The multiplexer was switched to channel 0. This was achieved by sending code

0000 to the address lines of the multiplexer circuit through the PPI device port A (PA0-PA3).

3) The output of the window detector circuit was read through the PPI device port B (PB0-PB2).

4) An appropriate gain which reflected the magnitude of the signal was selected.

5) The gain of the PGA was adjusted and the signal from the selected channel was digitised.

6) The output of the analogue to digital convertor was read. This together with the value of a code which represented the gain used for the PGA were stored in RAM.

7) If digitisation of signals from the 8 channels was not complete, the multiplexer was switched to the next channel and operations (3)-(6) were repeated.

References

Disk operating system technical reference manual, (1985), IBM Corporation.

Hall, D.V., (1988), "Microprocessors and interfacing, programming and hardware", McGraw-Hill.

IBM technical reference manual, (1985), "Personal computer hardware reference library", IBM corporation.

Chapter 5 Data Recording Procedure

20 schizophrenic patients, 16 PD patients, 11 HD patients, 21 AR of HD patients and 43 normal control subjects were enrolled for the study. The age and sex of the subjects were noted (the data associated with the age and sex of the subjects are shown together with the analysis results in chapters 7 and 8). All subjects were able to co-operate for the experiment. The severity of the symptoms in schizophrenic patients was measured (by Dr S. Oke) using the Diagnostic and Statistical Manual of Mental Disorders [DSM III, 1980]. Nine symptoms were measured. Each schizophrenic patient was given a score for each measured symptom. The scores varied between 0 (when the symptom was not observed) and 5 (when the symptom was severe). Table (5.1) shows the scores for the schizophrenic patients.

Table (5.1) The scores/or assessment of symptoms for schizophrenic patients.

Subject Number	Positive Symptoms				Negative Symptoms					Sum of Scores
	a	b	c	d	e	f	g	h	i	
1	0	2	0	0	2	0	4	4	2	14
2	4	4	0	0	0	1	0	0	0	9
3	4	4	4	2	2	2	3	3	3	27
4	4	4	0	0	3	3	4	4	2	24
5	4	3	2	0	4	3	4	4	2	26
6	0	0	0	0	0	0	4	4	2	10
7	0	0	3	0	2	4	4	4	2	19
8	0	0	3	0	4	4	5	4	3	23
9	0	0	3	0	4	3	4	4	3	21
10	3	0	4	2	4	3	5	4	4	29
11	0	0	0	0	4	2	4	2	2	14
12	0	0	2	0	0	4	4	4	4	18
13	0	0	0	0	3	2	4	2	1	12
14	0	0	0	0	3	3	4	4	2	16
15	2	5	4	0	0	0	1	2	0	14
16	0	0	0	0	2	4	4	4	3	17
17	0	4	0	0	0	0	0	4	0	8
18	3	4	4	0	3	4	4	4	3	29
19	0	0	0	2	2	4	4	3	3	18
20	0	0	0	0	4	4	4	4	3	19

Key:
a = hallucinations
b = delusions
c = bizarre behaviour
d = positive thought disorder
e = affective flattening
f = alogia
g = avolution-apathy
h = anhedonia-asociality
i = attention

The severity of disease in the HD and PD patients was assessed (by Dr E.M. Allen) using a grading scale which varied between 1 and 5. The grades are shown in Table (5.2).

Table (5.2) The severity of symptoms in HD and PD patients.

Grades	Number of Patients	
	HD Patients	PD Patients
1	2	1
2	1	2
3	0	1
4	5	12
5	3	0

Grade 1 included those newly diagnosed HD and PD patients for whom the disease had not affected their ability to lead a normal life (eg. they could work etc.). Grade 5 included those patients who had severe HD or PD and were totally dependent on others. The severity of the disease in patients classed as grades 2, 3 and 4 fell between grades 1 and 5, ie. those classed as grade 2 needed some assistance to lead a normal life, those classed as grade 3 could not live a normal life but they were self caring, and those classed as grade 4 needed significant help.

The names of the drugs for the patients who were on medication were noted (refer to Appendix (B)). The normal control subjects did not have any disorder which might have affected their CNV responses. The hardware and software used to record the data are described in chapters 3 and 4 respectively. The data were recorded in a normal EEG recording room. In order to minimise voltage drift, d.c. silver-silver chloride electrodes (see Figure (5.1)) were used for the recording of the CNV and EOG. The CNV was recorded from two sites using the linked earlobes as the reference. The CNV recording sites were the vertex (convexity of the scalp) and at a point on the midline approximately 30mm anterior to the vertex. Only the CNV data recorded from the vertex were analysed in this study. Four channels were allocated for the recording of EOG. The

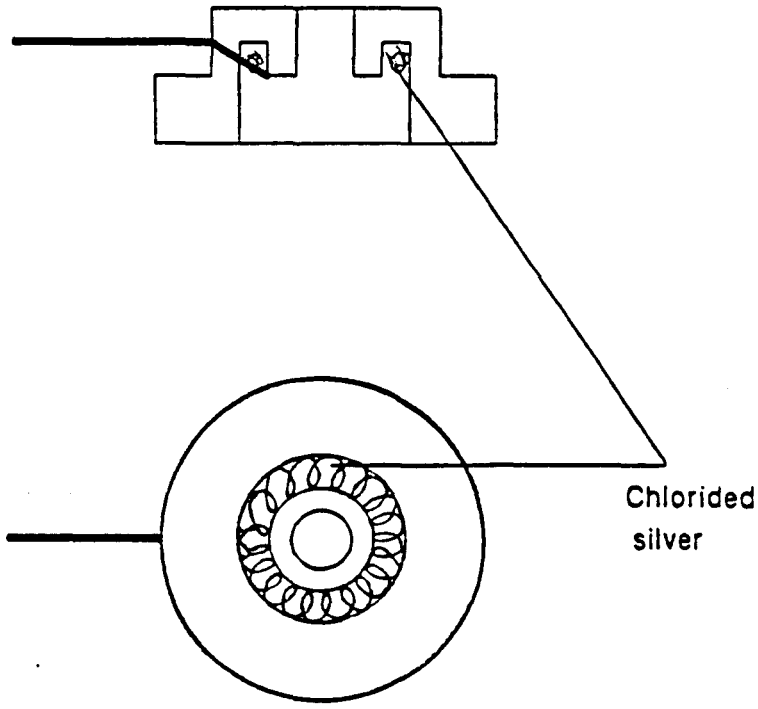


Figure 5.1 D.C. silver-silver chloride electrode.

electrode-pairs used for the EOG recordings are shown in Table (5.3). The positions of the EOG electrodes are shown in Figure (5.2).

Table (5.3) The symbols used for electro-oculogram electrodes.

Channel Number	Electro-oculogram (EOG)	Position of Electrodes
1	vertical left EOG	E_1-E_2
2	vertical right EOG	E_3-E_4
3	horizontal left EOG	E_5-E_6
4	horizontal right EOG	E_5-E_7

The electrodes were attached to the subjects using adhesive tape (for the facial electrodes) or glue (for the scalp electrodes). Each electrode was filled (through a hole at the centre of its cup) with "Neptic" electrode gel using a syringe which had a blunted needle. Whilst filling the electrodes, the blunted needle of the syringe was also used to abrade the skin under the electrodes. This reduced the impedance between the electrode and the skin. The impedances between an arbitrary electrode and all other electrodes were measured. If any impedance was more than 5kΩ the skin under the offending electrode was further abraded. The device used to measure the impedance indicated the modulus of the complex impedance at 13Hz. It was important to avoid using an impedance meter with a d.c. internal source as this would have caused a degradation of the electrode stability [Cooper et al., 1980].

The warning and imperative stimuli were a click and a 1kHz tone. On hearing the imperative stimulus, the subjects pressed a handheld push-button to terminate the tone. In order to familiarise the subjects with the experiment, 10 presentations (ie. 10 click and tone pairs) were made, initially with the subjects only listening.

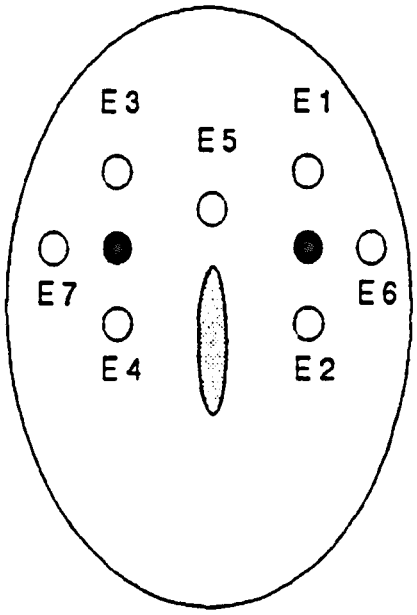


Figure 5.2 The positions of EOG electodes.

Then the subjects participated in 15 practice trials. Following that 32 CNV trials were recorded per subject.

The subjects' reaction times to the imperative stimulus were also measured. The sampling rate was 125Hz. The cut-off frequencies for the high-pass and low-pass filters in the hardware were 0.0159Hz and 30Hz respectively. The duration of each CNV trial was 12 seconds, corresponding to a 1 second pre-warning-stimulus section, a 1 second inter-stimulus interval and a 10 seconds post-imperative-stimulus section. The recording of the pre-warning-stimulus section was necessary for the baseline correction of the CNV (this procedure is described in chapter 6). Coelho [1988] investigated the effect of inter-stimulus interval duration on HD patients' identification. He compared the analysis results obtained when durations of the inter-stimulus interval were 1 and 4 seconds and suggested that duration of the inter-stimulus interval should be 1 second. The post-imperative-stimulus section was used for baseline correction of the CNV (refer to chapter 6) and a feature obtained from it was used in the identification of patients (this is described in chapter 8). The long period selected for the post-imperative-stimulus section ensured that the CNV had sufficient time to return to its baseline. The successive CNV trials were separated by a random interval which varied between 100ms and 400ms. The instrumentation system automatically rejected any faulty trials (a CNV trial was considered faulty if the subjects did not respond correctly to the imperative stimulus). The CNV trials grossly contaminated by ocular artefact in the sections of interest were also rejected. The instrumentation system had eight channels. The last two channels were allocated for the recording of the electrocardiogram (ECG) and the psychogalvanic response (PGR). The ECG was recorded by placing two ECG electrodes on the wrists of the subjects. The PGR electrodes were placed on the palm and the back of the subjects' hands.

Reference

DSM III, (1980), "Diagnosis and statistical manual of mental disorders", American Psychiatric Association, Third Edition, Washington DC.

Coelho, M., (1988), "Analysis of the CNV waveform in the time and frequency domains", M.Phil. thesis, Department of Electrical and Electronic Engineering, Sheffield City Polytechnic, Sheffield.

Cooper, R., Osselton, J.W. and Shaw, J.C., (1980), "EEG technology", Third edition, Butterworths, 20.

Chapter 6 Contingent Negative Variation Preprocessing Method

For the CNV to be clinically useful, it has to be preprocessed. The CNV preprocessing method used was originally developed by Nichols [1982] and then it was enhanced by Coelho [1988]. The method consisted of the following steps: mean level removal, baseline correction, digital low-pass filtering and ocular artefact removal. A description of each step follows.

6.1 Mean Level Removal

A d.c. offset (or mean level) can usually be observed in the CNV. This offset is mainly extracerebral in nature (eg. the skin potential) [Cooper et al., 1980] but the various components in the instrumentation system also contribute to it. It was desirable to have a baseline reference of zero so that comparisons over time could be made. Jervis et al. [1989] reported that the removal of d.c. offset from the CNV improved the effectiveness of the OA removal routines. As each CNV trial had a fixed duration, the d.c. offset was removed using,

$$x_{kr} = x_k - \frac{1}{N} \sum_{i=1}^{N} x_i \qquad \ldots(6.1)$$

where N is the number of samples per CNV trial, x_k is the k^{th} sample value and x_{kr} is the k^{th} sample value with the mean removed.

6.2 Baseline Correction

A side effect of the mean level removal was to cause a positive shift in the baselines of the pre- and post-stimulus sections of the CNV. It was therefore necessary to restore the true baseline. The mean of the pre-warning-stimulus section (y_{s1}) was calculated using,

$$y_{s1} = \frac{1}{P1} \sum_{i=1}^{P1} x_i \qquad \ldots(6.2)$$

where P1 is the sample number corresponding to the instant of the warning stimulus (S1) and x_i is the i^{th} sample value. Further-more, to allow for any small d.c. drift during the data acquisition, the mean signal level (y_{s2}) was also calculated from a point one second after the imperative-stimulus (S2) to the end of the CNV trial. The value of y_{s2} was subtracted from the same section (ie. the section from which y_{s2} was calculated). Thus,

$$y_{s2} = \frac{1}{N-P2-D} \sum_{i=P2+D}^{N} x_i \qquad \ldots(6.3)$$

where P2 is the sample number corresponding to the instant of S2, D is the delay after S2 which was set to 125 samples (this delay was necessary to avoid the auditory evoked potential due to S2) and N is the number of samples per CNV trial. The section between P1 and P2+D was corrected by subtracting y_{isi}, which was the appropriate fraction of the difference between y_{s1} and y_{s2}, therefore,

$$y_{isi} = \frac{y_{s2} - y_{s1}}{P2+D-P1} (k-P1) + y_{s1} \quad P1 \leq k \leq P2+D \qquad \ldots(6.4)$$

where k is the sample number.

6.3 Digital Low-pass Filtering

Digital low-pass filtering was necessary to filter out the unwanted high frequency components in the EEG. A finite impulse response (FIR) low-pass filter based on the design program of Rabiner and Gold [1977] was used for this purpose. FIR filters (unlike the infinite impulse response filters) do not distort the signals. The cut-off frequency of the digital low-pass filter used in the patients' identification

method as described in chapter 7 was 30Hz (filter length=21). This cut-off frequency had to be reduced to 7.5Hz (filter length=29) for use in the patients' identification methods described in chapters 8 and 9. The frequency response of the digital low-pass filter (cut-off frequency=7.5Hz) is shown in Figure (6.1). The reasons for selecting these cut-off frequencies were related to the particular methods of analysing the CNV and therefore they are discussed in the relevant chapters (ie. chapters 7 and 8).

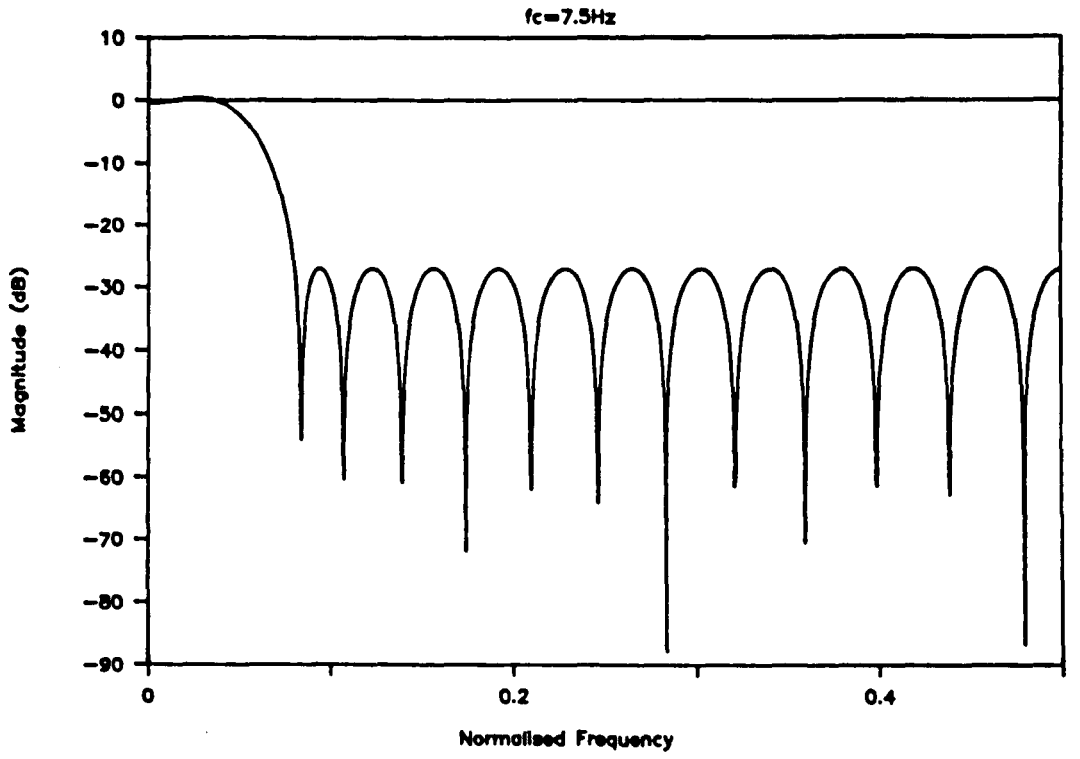
6.4 Ocular Artefact Removal

The eye has a positive cornea and a negative retina. This produces an electrical dipole. Whenever this electric field is changed due to the eye movement, eye rotation or blink, a change of potential develops around the eye. This potential is known as the electro-oculogram (EOG). The EOG spreads across the scalp to contaminate the EEG. The term OA is a collective reference given to a number eye-related potentials observed in the contaminated EEG. As the magnitude of the OA can be several hundred microvolts (compared to the magnitude of the CNV which is in the order of few microvolts), they are the main physiological sources of CNV contamination.

There are several methods of OA removal [Jervis et al., 1988]. Jervis et al. [1985] showed that a method known as proportional EOG subtraction was the most suitable technique and therefore it was selected. This method of OA removal was based on the assumptions that the measured EOGs had negligible cross-correlation with the true EEG and the OA was a linear combination of the selected EOGs. The formula used for removing OA removal was,

$$EEG_c(i) = EEG_m(i) - (\theta_1 HR(i)HL(i) + \theta_2 VR(i) + \theta_3 HL(i) + \theta_4 HR(i))$$

$$1 \leq i \leq N \qquad \ldots(6.5)$$




```
H(  1) = -0.98306499E-02 = H(  29)
H(  2) = -0.32145083E-01 = H(  28)
H(  3) = -0.12244012E-01 = H(  27)
H(  4) = -0.19535918E-01 = H(  26)
H(  5) = -0.13696495E-01 = H(  25)
H(  6) = -0.71664676E-02 = H(  24)
H(  7) =  0.44455901E-02 = H(  23)
H(  8) =  0.19459262E-01 = H(  22)
H(  9) =  0.37399143E-01 = H(  21)
H( 10) =  0.56883872E-01 = H(  20)
H( 11) =  0.76271415E-01 = H(  19)
H( 12) =  0.93765736E-01 = H(  18)
H( 13) =  0.10773635E+00 = H(  17)
H( 14) =  0.11673015E+00 = H(  16)
H( 15) =  0.11983693E+00 = H(  15)
```

Figure 6.1 Digital low-pass filter frequency response (cut-off frequency = 7.5Hz).

where EEG_c, EEG_m, HL(i), HR(i) and VR(i) are the i^{th} sample values of the corrected EEG, measured EEG, horizontal left EOG, horizontal right EOG and vertical right EOG respectively. N is the number of samples per CNV trial and $\Theta_1 \ldots \Theta_4$ are the transmission coefficients. This formula allowed for the effects of the vertical and horizontal eye movements and is the model recommended by Jervis et al. [1989]. The values of $\Theta_1 \ldots \Theta_4$ were calculated off-line by a correlation technique described by Quilter et al. [1977].

6.5 Description of the Preprocessed Plots

Figures (6.2)-(6.5) show the vertical left, vertical right, horizontal left and horizontal right EOGs. The OA potentials can be seen in the EOG plots in the time period between t=7 to t=11 seconds. A single CNV trial prior to the preprocessing is shown in Figure (6.6). The OA potentials have contaminated the CNV (this is visible in the time period between t=7 to t=11 seconds). The effect of OA contamination has been greatly reduced in the CNV trial following the preprocessing (Figure (6.7)).

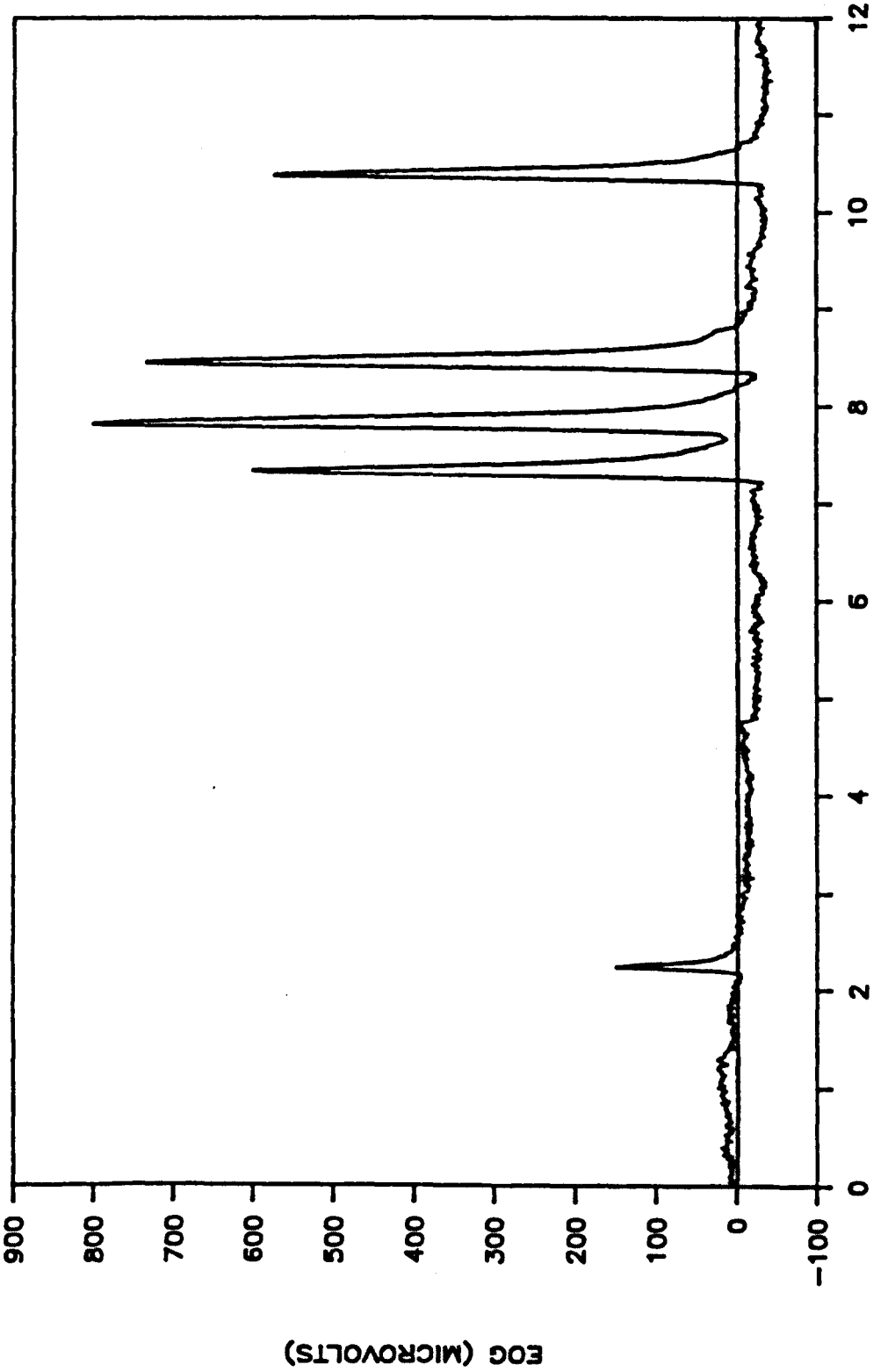


Figure 6.2 Vertical left EOG.

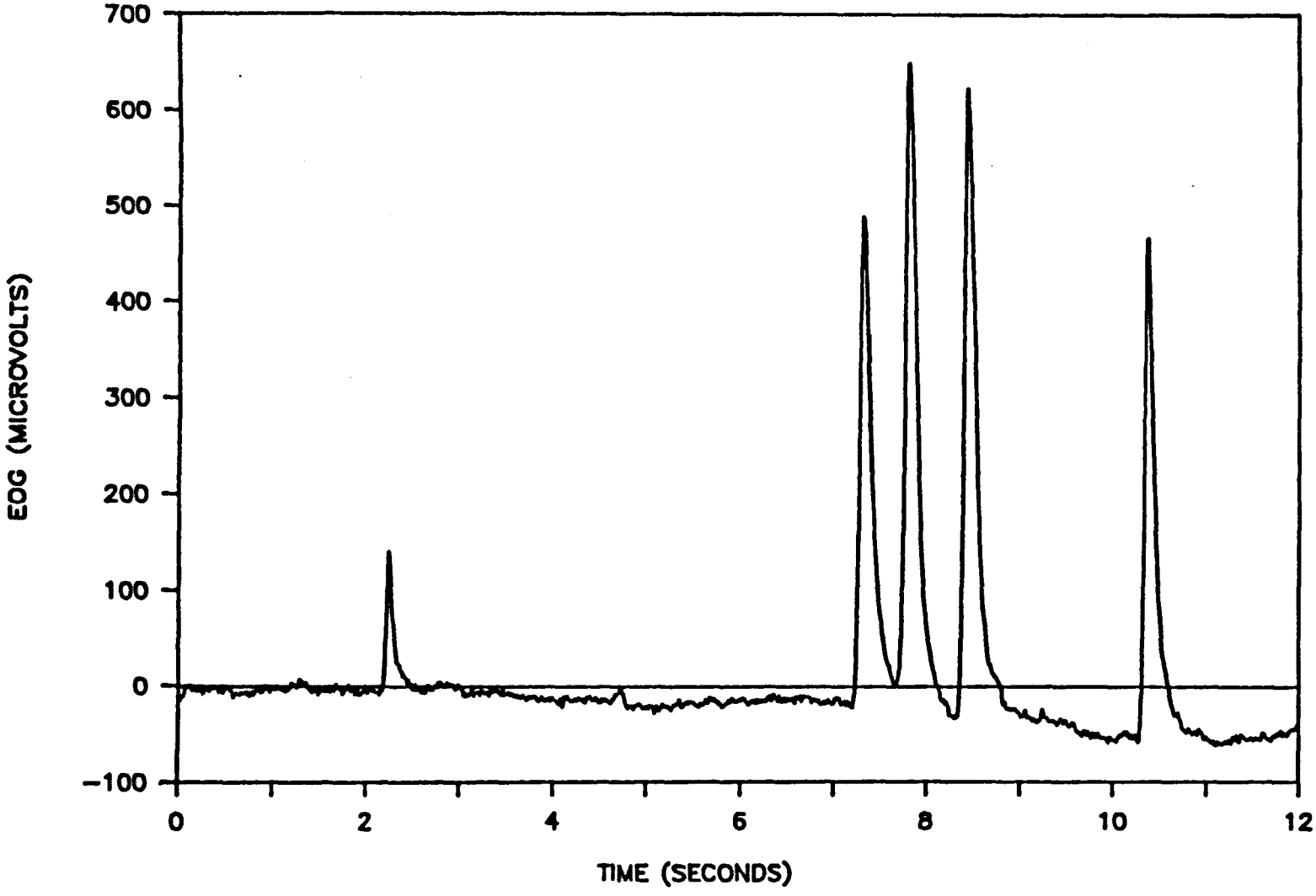


Figure 6.3 Vertical right EOG.

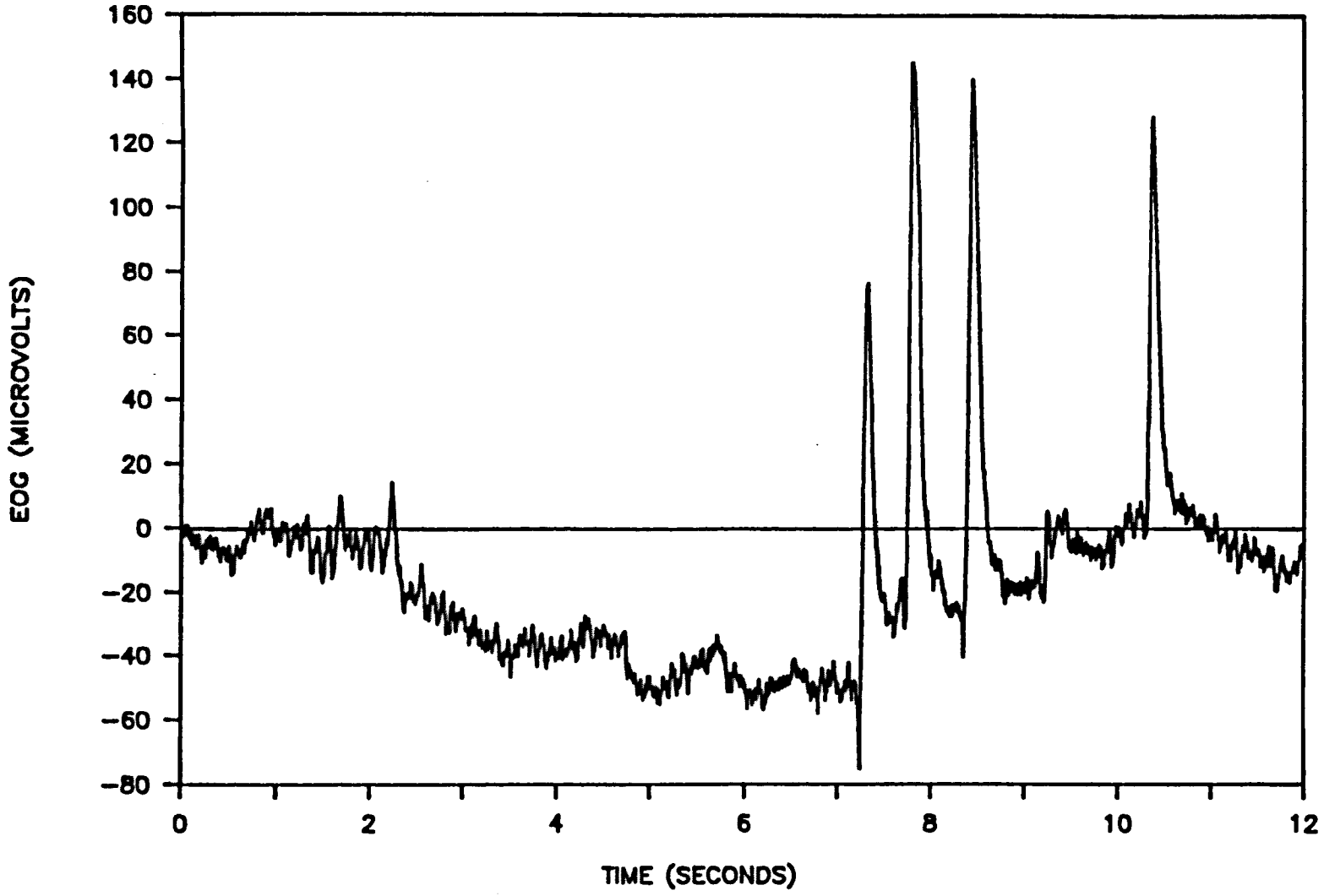


Figure 6.4 Horizontal left EOG.

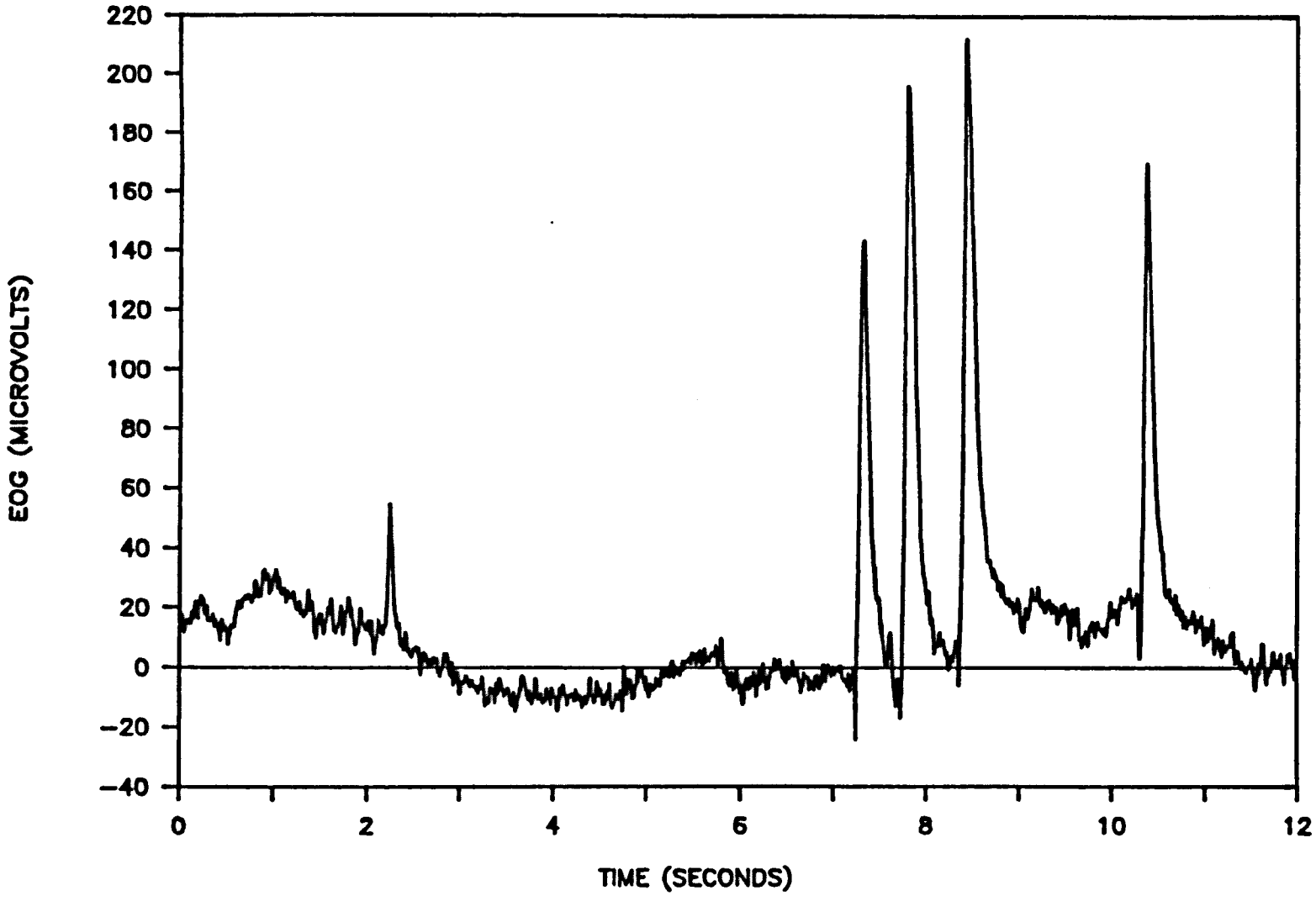


Figure 6.5 Horizontal right EOG.

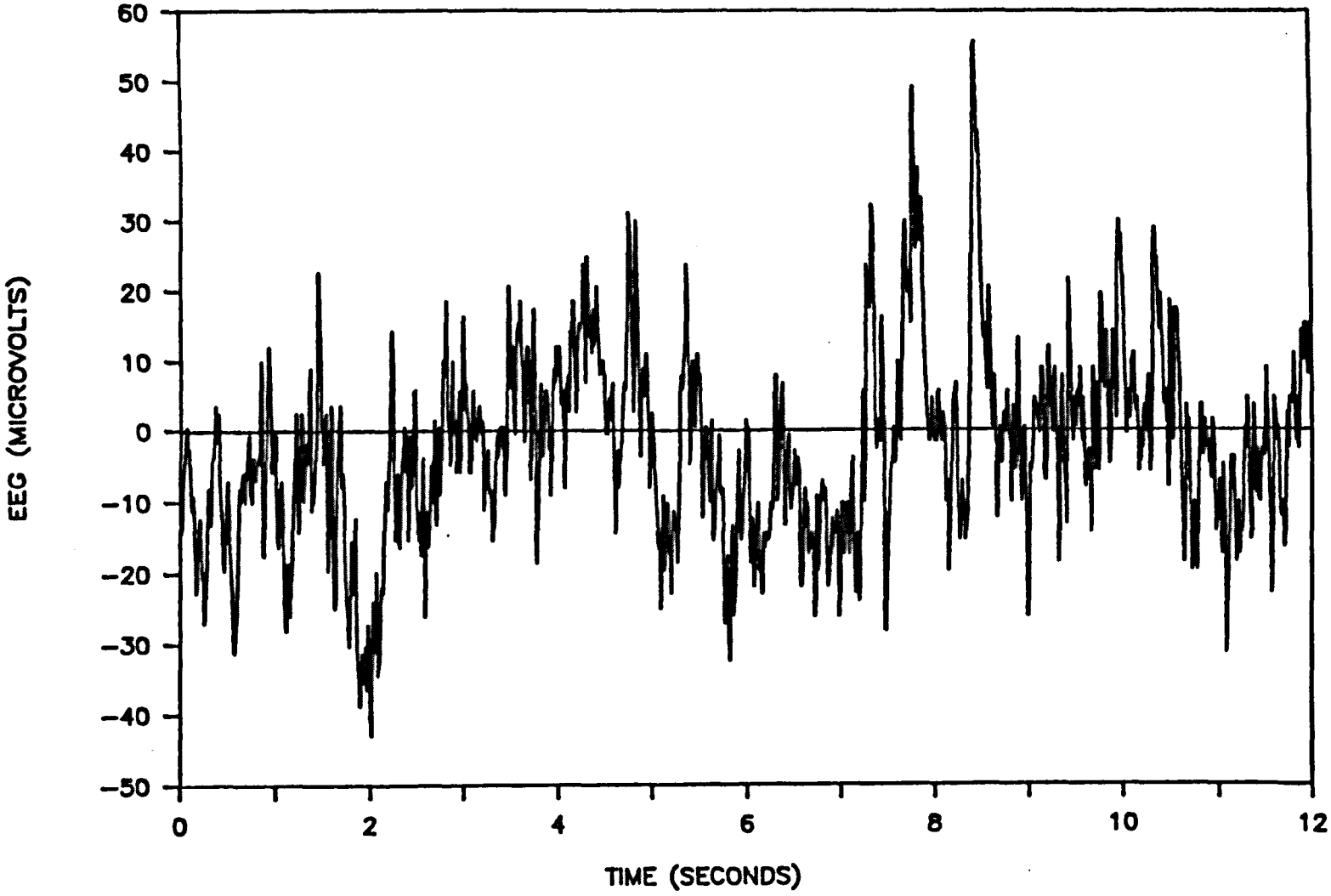


Figure 6.6 A CNV response before preprocessing.

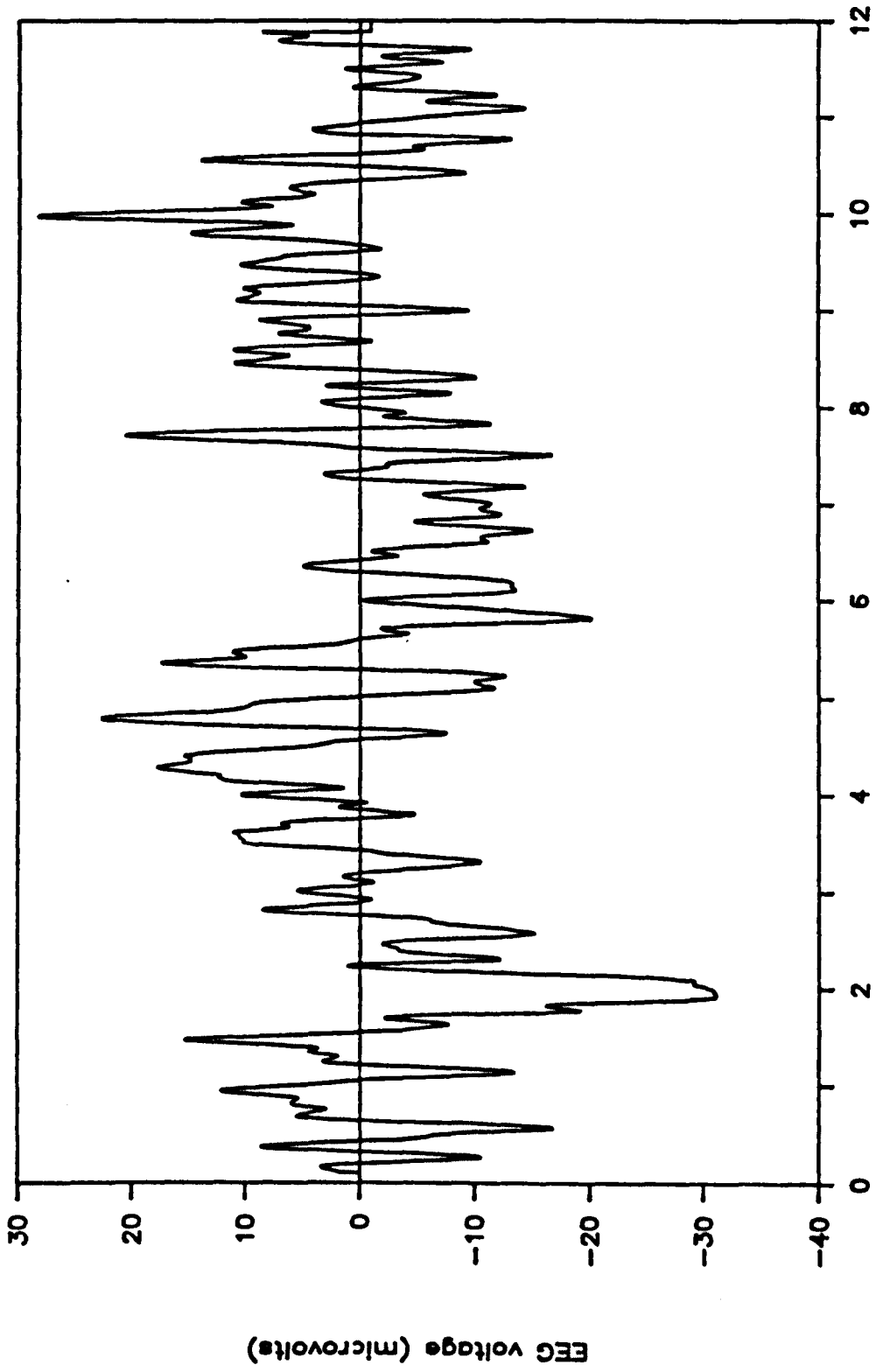


Figure 6.7 A CNV response after preprocessing.

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Jervis, B.W., Ifeachor, E.C. and Allen, E.M., (1988), "The removal of ocular artefacts from the electroencephalogram: a review", Medical and Biological Engineering and Computing, 6:2-12.

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Quilter, P.M., MacGillivray, B.B. and Wadbrook, D.G., (1977), "The removal of eye movement artefact from EEG signals using correlation techniques", IEE conference publication, No.159, 93-100.

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Chapter 7 Identification of Schizophrenic, PD and HD Patients by Frequency Analysis and Discriminant Analysis of the CNV

In order to investigate the composition of evoked potentials, Nichols [1982] and Jervis et al. [1983] applied a series of statistical tests to the harmonic frequency components of the auditory evoked potentials and the CNV responses of a number of normal subjects and Huntington's disease (HD) patients. Jervis et al. [1984] envisaged that it might be possible to distinguish between HD patients and normal subjects using the techniques generated. They applied the four statistical tests to the first six CNV harmonic frequency components of eight HD patients, six normal subjects and three "at-risk" (AR) of HD patients. The statistical tests were:

- Nearest and furthest mean amplitude test,
- Pre- and post-stimulus mean amplitude difference test,
- Rayleigh test of circular variance,
- Modified Rayleigh test of circular variance.

The above four statistical tests are described in section 7.1.1. Jervis et al. [1984] used the variables obtained from the application of the four tests to the first six CNV harmonic frequency components in a logical flow chart. Using this flow chart they identified the majority of HD patients from normal subjects and suggested that one of the AR of HD patients would develop HD. Some of the problems associated with the use of flow chart for this purpose were as follows:

i) It was not possible to differentiate between the HD patients and normal subjects whenever the application of the statistical tests to the CNV harmonic frequency components did not give any statistically significant result. This was the case for two of the HD patients.

ii) As the flow chart was designed by considering the CNV data from a limited number of individuals, a review of its structure was necessary following the inclusion of data from other HD patients and normal subjects.

In an attempt to overcome the problems associated with the use of the flow chart, Coelho [1988] selected a set of harmonic frequency components by considering the averaged CNV energy spectrum plots of eight HD patients and six normal subjects (the CNV responses of these individuals were previously recorded by Nichols). He then applied the four statistical tests (referred to earlier) to the CNV harmonic frequency components and used the resulting variables in a stepwise discriminant analysis (SDA) program. The SDA program identified one variable among those variables as being most discriminatory. Coelho used this variable in a discriminant analysis (DA) program. Although he was able to identify the HD patients, his results had to be treated with caution as the DA program was calibrated and then tested on the data from the same individuals. For the assessment of the effectiveness of the method it is necessary to calibrate and test the DA program on the CNV responses from a different set of individuals [Grimsley, 1989].

In this study the method developed by Coelho [1988] was applied to a larger number of HD patients and normal subjects and it was extended to differentiate between:

- Parkinson's disease (PD) patients and normal subjects.
- Schizophrenic patients and normal subjects.
- HD patients and PD patients.
- HD patients and schizophrenic patients.
- PD patients and schizophrenic patients.

To evaluate the effectiveness of the method, a leave-one-out procedure was used. This ensured the CNV responses from individuals included during the DA program calibration phase were excluded in the test phase.

A description of the procedure used to identify the patients follows.

7.1 Generation of Variables

32 CNV trials recorded from each individual were preprocessed as described in chapter 6. Two segments from each preprocessed CNV trial were analysed. The segments were:

i) A 512ms segment prior to the imperative-stimulus (post-stimulus segment). This segment contains the CNV components which share features with the readiness potential and its nature is related to the dynamics of the motor response [Rohrbaugh, et al., 1976].

ii) A 512ms segment prior to the warning-stimulus (pre-stimulus segment). The comparison of this segment with the post-stimulus segment allowed detection of possible amplitude and phase changes in the harmonic frequency components of the CNV in the patients and normal subjects. These changes develop as a result of the onset of the warning- and imperative-stimuli.

Each selected segment contained 64 sample values. The next step was to transform the data segments into the frequency domain using the discrete Fourier transform (DFT). But prior to this operation, the segments were windowed and then augmented with zeros. The windowing was necessary in order to reduce the spectral leakage. Spectral leakage develops because the energy in the original spectral components leaks to the other frequency components after truncation in

the time domain [Stark and Tuteur, 1979]. This can distort the frequency spectrum by introducing spurious peaks and cancelling out the true peaks. Coelho [1988] after investigating the performance of several windows on simulated data and the CNV responses suggested the use of the Kaiser-Bessel window. The trade-off between the side-lobes level and main-lobe width of a spectrum after it is subjected to the Kaiser-Bessel window is determined by a parameter, α [Harris, 1978]. Coelho [1988] found that when $\alpha=0.75$ it produced an acceptable compromise. Therefore the two segments were subjected to the Kaiser-Bessel window, using $\alpha=0.75$. Following the DFT, any signal components which occur at a frequency between two adjacent harmonic frequency components will have its energy shared and thus distort the amplitude of the adjacent harmonic components. To reduce this effect the DFT harmonic separation was reduced by using augmenting zeros before the transformation. After the zero augmentation, each segment contained 64 CNV sample values and 960 zeros. The number of data points for the DFT had to conform to 2^n, where n is an integer. In this case n was equal to 10, providing 1024 points.

The four statistical tests were applied to the first 96 harmonic frequency components of the two frequency spectra (ie. the spectra of the pre- and post-stimulus segments) . The first 96 harmonic frequency components represented the frequency range 0 to 11.72Hz (ie. 96 / (1024/64) x 1 / (64 x 0.008) = 11.72Hz). Jervis et al. [1989] by Fourier analysis of the simulated CNV showed that most of the CNV energy was concentrated below 1Hz and its energy spectral density fell to -60dB at about 5Hz. Therefore the first 96 frequency harmonics were sufficient for this analysis.

7.1.1 Description of the Statistical Tests Applied to the CNV Harmonic Frequency Components

As mentioned in section 7.1 four statistical tests were applied to the selected CNV

harmonic frequency components. A description of these tests follows.

7.1.2 Nearest and Furthest Mean Amplitude Test

This test was designed for analysing the variation of amplitude with phase angle in the post-stimulus spectrum. As 32 CNV trials were recorded per subject, this produced 32 post-stimulus spectra. For each post-stimulus spectrum the magnitude (length) of the n^{th} selected frequency harmonic was obtained. The mean length of that half of the vectors whose angles were within the smallest arc was calculated. This was repeated for the remaining vectors. A one-tailed t-test was then performed to determine whether the former mean was greater than the latter. The resulting value of the t-test was used as a variable. The above procedure was repeated for the remaining selected harmonic frequency components.

7.1.3 Pre- and Post-Stimulus Mean Amplitude Difference Test

The differences between corresponding pre- and post-stimulus phasor lengths for the n^{th} selected harmonic frequency component of each of the 32 trials were calculated. The mean of the differences was computed. Using a two-tailed t-test, this mean was tested to determine whether it was significantly different from zero. The value of the resulting t-test was used as a variable. This procedure was repeated for the remaining selected harmonic frequency components.

7.1.4 The Rayleigh Test of Circular Variance

This test was applied to the phase angles in the 32 post-stimulus spectra for each selected CNV harmonic frequency component to determine whether the phase angles ($\Theta_1 \ldots \Theta_N$) were distributed in a non-uniform manner. The circular variance, S_o is given by [Mardia, 1972],

$$S_o = 1 - \bar{R} \qquad \ldots(7.1)$$

$$\bar{R} = [\bar{C}^2 + \bar{S}^2]^{\frac{1}{2}} \qquad \ldots(7.2)$$

$$\bar{C} = \frac{1}{N} \sum_{i=1}^{N} \cos\theta_i \qquad \ldots(7.3)$$

$$\bar{S} = \frac{1}{N} \sum_{i=1}^{N} \sin\theta_i \qquad \ldots(7.4)$$

If the phase angles $\theta_1 = \theta_2 \ldots = \theta_N = \theta$ then $\bar{C} = \cos\theta$ and $\bar{S} = \sin\theta$. This gives,

$$\bar{R} = [\cos^2\theta + \sin^2\theta]^{\frac{1}{2}} = 1 \qquad \ldots(7.5)$$

and $$S_o = 0 \qquad \ldots(7.6)$$

This corresponds to the case where all the phase angles have the same value. Alternatively, when the phase angles are distributed uniformly over the range 0 to 2π then the values of $\bar{R}$ and S_o become,

$$\bar{R} = 0 \qquad \ldots(7.7)$$

$$S_o = 1 \qquad \ldots(7.8)$$

The value of S_o was used as a variable.

7.1.5 The Modified Rayleigh Test of Circular Variance

The modified Rayleigh test of circular variance encompassed both the amplitudes and the phase angles in the post-stimulus spectrum. For each selected harmonic frequency component, 32 vectors (one for each CNV trial) were obtained. The vectors were ranked in ascending order of magnitudes. Then the test was carried out using,

$$U_o = 1 - \left[\left[\frac{\sum_{i=1}^{N} R_i \cos\theta}{\sum_{i=1}^{N} R_i} \right]^2 + \left[\frac{\sum_{i=1}^{N} R_i \sin\theta_i}{\sum_{i=1}^{N} R_i} \right]^2 \right]^{\frac{1}{2}} \quad \ldots(7.9)$$

where R_i is the rank of the i^{th} phasor. U_o is closely related to the statistic R^* proposed by Moore [1980]. The value of U_o was used as a variable.

7.2 Variable Reduction Procedure

The application of the four statistical tests to the first 96 harmonic frequency components resulted in 384 variables (ie. 96 harmonics x 4 tests = 384 variables). In order to identify the most discriminatory variables a series of tests were carried out using the Statistical Analysis Systems (SAS) [1982 and 1985] packages. A brief description of the tests follows.

7.2.1 Normal Distribution Test

A test for the statistical distribution of the variables was necessary as the succeeding procedures required the variables to have normal or approximately normal distributions.

This test was carried out using the SAS procedure, Univariate. It computed a test statistic for the null hypothesis that the variables were from the normal distribution. It calculated the Shapiro-Wilk statistic, W [Shapiro and Wilk, 1965] and provided a probability value indicating whether the hypothesis should be accepted or rejected (the significance level was 5%). The Univariate procedure also plotted the variables together with a curve indicating where normally

distributed data would fall. The variables found not to be normally distributed were excluded from further analysis.

7.2.2 T-test

This was a two-tailed t-test for testing the hypothesis that the means of the variables from the two groups (ie. patients from a category against their normal control subjects or against the patients from another category) were equal. It computed the t-statistic based on the assumption that the variances from the two groups were equal. It also calculated an approximate t based on the assumption that the variances were unequal. For each test the degrees of freedom and probability level were computed. Satterthwaite's approximation [Satterthwaite, 1946] was used to determine the approximate t. A folded (F) statistic [Steel and Torrie, 1980] was computed to test for equality of the two variances. The significance levels for the t-test and F-statistic test were 10% and 5% respectively.

7.2.3 Stepwise Discriminant Analysis

The variables selected from the previous steps were used in the SAS stepwise discriminant analysis program, Stepdisc. This program selected a subset of the variables in order to form a good discrimination model using stepwise selection. The variables selected by this program are shown in Table (7.1).

Table (7.1) The variables used to identify subjects.

H_xT_y represents test y applied to harmonic x, where
T_1 = nearest and furthest mean amplitude test,
T_2 = pre- and post-stimulus mean amplitude difference test,
T_3 = Rayleigh test of circular variance and
T_4 = modified Rayleigh test of circular variance.

Categories	Discriminatory Variables
Huntington's disease patients vs. normal control subjects	$H_{14}T_3$, $H_{26}T_2$, $H_{71}T_1$
schizophrenic patients vs. normal control subjects	H_3T_3, H_5T_3, $H_{58}T_1$, $H_{72}T_4$ $H_{85}T_3$, $H_{88}T_1$
Parkinson's disease patients vs. normal control subjects	H_6T_1, $H_{18}T_3$, $H_{26}T_1$, $H_{37}T_4$ $H_{63}T_3$, $H_{86}T_1$, $H_{91}T_4$
Huntington's disease patients vs. schizophrenics	$H_{24}T_2$, $H_{28}T_2$, $H_{67}T_3$, $H_{72}T_1$ $H_{76}T_1$
Huntington's disease vs. Parkinson's disease patients	$H_{20}T_2$, $H_{38}T_1$, $H_{83}T_3$, $H_{93}T_2$
schizophrenics vs. Parkinson's disease patients	$H_{13}T_2$, $H_{26}T_2$, $H_{38}T_1$, $H_{72}T_1$

7.3 Discriminant Analysis

The classification of the individuals was carried out using discriminant analysis (DA). DA is a technique for classifying individuals into mutually exclusive and exhaustive groups on the basis of a set of independent variables. Only the case involving the identification of one group from another group was considered. In the linear DA method, the discriminant score for each individual is obtained using,

$$Y = b'X \qquad \ldots(7.10)$$

where Y is a 1xn vector of discriminant scores, b' is a 1xp vector of discriminant weights (note the symbol ' indicates transpose), and X is a pxn matrix containing the values for each of the n individuals of the p independent variables. To assign the individuals, the discriminant weight vector needs to be computed. It has been shown [Morrison, 1976],

$$b = S^{-1}(\bar{x}_1 - \bar{x}_2) \qquad \ldots(7.11)$$

where $\bar{x}_1$ and $\bar{x}_2$ are the mean vectors obtained from the data matrices, and S^{-1} is the inverse of the pooled sample variance-covariance matrix and is obtained using [Morrison, 1976],

$$S = \frac{1}{n_1 + n_2 - 2}(x'_1x_1 + x'_2x_2) \qquad \ldots(7.12)$$

The number of individuals in each group is represented by n_1 and n_2. x_1 is the (pxn_1) mean corrected data matrix taken from group 1 and x_2 is the (pxn_2) mean corrected matrix taken from group 2.

A formula for assigning the individuals to one of the two groups based on the above information is [Morrison, 1976],

$$W = x'b - \tfrac{1}{2}(\bar{x}_1 + \bar{x}_2)'b \qquad \ldots(7.13)$$

The individuals are assigned to group 1 if W is greater than 0 otherwise to group 2. The DA program provided by SAS, Discrim, gave the probabilities which indicated to which group an individual belonged.

Initially the patients from each category (schizophrenia, PD and HD) were age and

sex matched with their normal control subjects and their CNV variables were processed by the DA program. Then the patients with HD were age and sex matched (as closely as it was possible) with schizophrenic patients and their variables were processed by the DA program. This was repeated for HD and PD patients, and PD and schizophrenic patients. To make best use of the recorded data, a leave-one-out approach was followed. In this method the variables of n-1 individuals (n is the number of individuals in a patient category and their normal control subjects or the patients from another category) were used in the DA program. The DA program used this data to setup a classification rule (ie. the calibration phase). Then the resulting information together with the variables from the individual not included in the calibration phase were used by the DA program. This generated a probability value which indicated to which group the individual belonged. This was repeated n times (for example, for the 20 schizophrenic patients and their 20 normal control subjects, this procedure was repeated 40 times).

7.4 Results and Discussion

Tables (7.2a) to (7.2f) show the probabilities obtained following the application of the DA program.

Table (7.2a) Schizophrenic patient versus normal control subjects. P(S) and P(N) represent the probabilities that an individual is schizophrenic or normal respectively.

Schizophrenic Patients			Normal Control Subject		
Subject Number	P(S)	P(N)	Subject Number	P(S)	P(N)
1	1.0000	0.0000	21	0.0000	1.0000
2	0.5753	0.4247	22	0.0477	0.9523
3	0.9998	0.0002	23	0.0011	0.9989
4	1.0000	0.0000	24	0.0000	1.0000
5	0.9366	0.0634	25	0.0184	0.9816
6	0.9948	0.0052	26	0.0001	0.9999
7	0.9016	0.0984	27	0.0049	0.9951
8	1.0000	0.0000	28	0.2197	0.7803
9	0.8269	0.1731	29	0.0000	1.0000
10	1.0000	0.0000	30	0.0002	0.9998
11	0.9968	0.0032	31	0.0047	0.9953
12	1.0000	0.0000	32	0.0164	0.9836
13	0.9999	0.0001	33	0.0010	0.9990
14	0.9952	0.0048	34	0.0000	1.0000
15	1.0000	0.0000	35	0.0001	0.9999
16	0.9883	0.0117	36	0.0051	0.9949
17	0.4600	0.5400	37	0.0000	1.0000
18	1.0000	0.0000	38	0.0003	0.9997
19	0.8960	0.1040	39	0.0436	0.9564
20	0.9993	0.0007	40	0.1739	0.8261

Table (7.2b) Parkinson's disease patients versus normal control subjects. P(P) and P(N) represent the probabilities that an individual has PD or is normal respectively.

Parkinson's Disease Patients			Normal Control Subject		
Subject Number	P(P)	P(N)	Subject Number	P(P)	P(N)
1	0.6857	0.3143	17	0.0083	0.9917
2	0.9975	0.0025	18	0.0000	1.0000
3	1.0000	0.0000	19	0.3193	0.6807
4	0.8060	0.1940	20	0.0008	0.9992
5	0.9990	0.0010	21	0.0837	0.9163
6	0.9401	0.0599	22	0.0005	0.9995
7	0.8316	0.1684	23	0.0001	0.9999
8	0.8445	0.1555	24	0.8776	0.1224
9	0.9982	0.0018	25	0.0004	0.9996
10	0.1969	0.8031	26	0.0049	0.9951
11	0.9995	0.0005	27	0.0001	0.9999
12	0.9995	0.0005	28	0.0000	1.0000
13	0.9996	0.0004	29	0.0037	0.9963
14	0.9905	0.0095	30	0.0003	0.9997
15	1.0000	0.0000	31	0.0024	0.9976
16	1.0000	0.0000	32	1.0000	0.0000

Table (7.2c) Huntington's disease patients versus normal control subjects. P(H) and P(N) represent the probabilities that an individual has HD or is normal respectively.

Huntington's Disease Patients			Normal Control Subjects		
Subject Number	P(H)	P(N)	Subject Number	P(H)	P(N)
1	0.8493	0.1507	12	0.0002	0.9998
2	1.0000	0.0000	13	0.0005	0.9995
3	0.9963	0.0037	14	0.0000	1.0000
4	1.0000	0.0000	15	0.0000	1.0000
5	1.0000	0.0000	16	0.0000	1.0000
6	0.9998	0.0002	17	0.0000	1.0000
7	0.9998	0.0002	18	0.4313	0.5687
8	0.9971	0.0029	19	0.0030	0.9970
9	0.9507	0.0493	20	0.0000	1.0000
10	1.0000	0.0000	21	0.0001	0.9999
11	0.9999	0.0001	22	0.0231	0.9769

Table (7.2d) Huntington's disease patients versus schizophrenic subjects. P(H) and P(S) represent the probabilities that an individual has HD or is schizophrenic respectively.

Huntington's Disease Patients			Schizophrenic Patients		
Subject Number	P(H)	P(S)	Subject Number	P(H)	P(S)
1	0.9999	0.0001	12	0.0000	1.0000
2	0.9742	0.0258	13	0.0000	1.0000
3	1.0000	0.0000	14	0.0000	1.0000
4	1.0000	0.0000	15	0.0001	0.9999
5	1.0000	0.0000	16	0.0001	0.9999
6	1.0000	0.0000	17	1.0000	0.0000
7	1.0000	0.0000	18	0.0000	1.0000
8	1.0000	0.0000	19	0.4477	0.5523
9	1.0000	0.0000	20	0.0000	1.0000
10	1.0000	0.0000	21	0.0000	1.0000
11	1.0000	0.0000	22	0.0000	1.0000

Table (7.2e) Schizophrenic patients versus Parkinson's disease patients. P(S) and P(P) represent the probabilities that an individual is schizophrenic or has PD.

Schizophrenic Patients			Parkinson's Disease Patients		
Subject Number	P(S)	P(P)	Subject Number	P(S)	P(P)
1	0.9993	0.0007	17	0.0153	0.9847
2	1.0000	0.0000	18	0.0010	0.9990
3	0.9812	0.0188	19	0.0197	0.9803
4	0.9999	0.0001	20	0.9940	0.0060
5	0.3456	0.6544	21	0.0275	0.9725
6	0.9824	0.0176	22	0.0009	0.9991
7	0.9987	0.0013	23	0.0000	1.0000
8	0.9365	0.0635	24	0.0379	0.9621
9	0.9998	0.0002	25	0.0175	0.9825
10	0.8068	0.1932	26	0.0409	0.9591
11	0.9993	0.0007	27	0.0003	0.9997
12	0.9999	0.0001	28	0.0000	1.0000
13	0.2775	0.7225	29	0.0000	1.0000
14	0.3056	0.6944	30	0.0000	1.0000
15	0.9973	0.0027	31	0.0079	0.9921
16	0.9995	0.0005	32	0.1398	0.8602

Table (7.2f) Huntington's disease patients versus Parkinson's disease patients. P(H) and P(P) represent the probabilities that an individual has HD or PD.

Huntington's Disease Patients			Parkinson's Disease Patients		
Subject Number	P(H)	P(P)	Subject Number	P(H)	P(P)
1	0.9999	0.0001	12	0.7003	0.2997
2	0.9834	0.0166	13	0.0001	0.9999
3	0.9993	0.0007	14	0.0005	0.9995
4	1.0000	0.0000	15	0.0000	1.0000
5	0.9999	0.0001	16	0.9642	0.0358
6	0.9981	0.0019	17	0.0003	0.9997
7	0.2019	0.7981	18	0.0000	1.0000
8	0.9997	0.0003	19	0.0201	0.9799
9	0.8555	0.1445	20	0.0001	0.9999
10	1.0000	0.0000	21	0.0000	1.0000
11	0.9995	0.0005	22	0.0000	1.0000

As in each analysis the number of individuals in the two groups were equal, ie. $n_1 = n_2$, a probability threshold value of 0.5 was used. Therefore if the probability was less than 0.5, the individual belonged to one group, otherwise the individual belonged to the other group. In Table (7.2a) the probabilities of schizophrenic patients versus normal subjects are shown. As can be observed all normal subjects were identified correctly. One schizophrenic patient (subject number 17) was misclassified as normal. Table (7.2b) indicates the probabilities for the PD patients versus normal subjects. A PD patient (subject number 10) and two normal subjects (subject numbers 24 and 32) were classified into the wrong group. Table (7.2c) shows the probabilities for the HD patients versus normal subjects. Every one in these categories was classified correctly. The probabilities of the HD patients versus schizophrenic patients are shown in Table (7.2d). Every HD patient was placed in the correct group but a schizophrenic patient (subject number 17) was misclassified. Table (7.2e) indicates the probabilities for schizophrenic patients versus PD patients. Three schizophrenic patients (subject numbers 5, 13, and 14) were misclassified. One of the PD (subject number 20) patients was also

placed in a wrong category. Table (7.2f) shows the probabilities for the HD patients versus PD patients. An HD patient (subject number 7) and two PD patients (subject numbers 12 and 16) were misclassified.

The overall performance of the method in differentiating between the patients and normal subjects, and between the patients of different categories is included in Tables (7.3a) to (7.3f).

Table (7.3a) The subjects' details and overall differentiation success rate for Huntington's disease versus normal control subjects.

Parameters		Subjects' Categories	
		Huntington's Disease	Control Subjects
number of subjects	total	11 (6 male)	11 (6 male)
	on drug	5	0
age	mean	53.73	50.09
	STD	10.97	10.53
	range	39 to 77	40 to 73
differentiation success rate in the test domain		100%	100%

Table (7.3b) The subjects' details and overall differentiation success rate for schizophrenic patients versus normal control subjects.

Parameters		Subjects' Categories	
		Schizophrenic Patients	Control Subjects
number of subjects	total	20 (15 male)	20 (15 male)
	on drug	18	0
age	mean	33.60	39.50
	STD	12.22	13.66
	range	20 to 68	22 to 75
differentiation success rate in the test domain		95.0%	100%

Table (7.3c) The subjects' details and overall differentiation success rate for Parkinson's disease patients versus normal control subjects.

Parameters		Subjects' Categories	
		Parkinson's Disease	Control Subjects
number of subjects	total	16 (10 male)	16 (10 male)
	on drug	12	0
age	mean	63.63	50.81
	STD	9.68	11.16
	range	42 to 80	35 to 75
differentiation success rate in the test domain		93.8%	87.5%

Table (7.3d) The subjects' details and overall differentiation success rate for Huntington's disease patients versus schizophrenic patients.

Parameters		Subjects' Categories	
		Huntington's Disease	Schizophrenic Patients
number of subjects	total	11 (6 male)	11 (7 male)
	on drug	5	9
age	mean	53.73	40.64
	STD	10.93	12.34
	range	39 to 77	27 to 68
differentiation success rate in the test domain		100%	90.91%

Table (7.3e) The subjects' details and overall differentiation success rate for Huntington's disease patients versus Parkinson's disease patients.

Parameters		Subjects' Categories	
		Huntington's Disease	Parkinson's Disease
number of subjects	total	11 (6 male)	11 (6 male)
	on drug	5	9
age	mean	53.73	60.91
	STD	10.97	10.52
	range	39 to 77	42 to 80
differentiation success rate in the test domain		90.91%	81.82%

Table (7.3f) The subjects' details and overall differentiation success rate for schizophrenic patients versus Parkinson's disease patients.

Parameters		Subjects' Categories	
		Schizophrenic Patients	Parkinson's Disease
number of subjects	total	16 (12 male)	16 (10 male)
	on drug	14	12
age	mean	36.63%	63.63%
	STD	11.83	9.68
	range	25 to 68	42 to 80
differentiation success rate in the test domain		81.25%	93.75%

The overall success rates were not always 100%. This could be because the CNV responses in some of the patients were not significantly different from the CNV responses in the normal subjects. When differentiating between the individuals from a patient category from another patient category (ie. HD patients versus PD patients, HD patients versus schizophrenic patients, and PD patients versus schizophrenic patients), it was not possible to age and sex match the individuals closely (this was mainly because the general ages of onset of the above disorders are different). This may have reduced success rates in differentiating between patient groups.

7.5 Conclusion

The results obtained in this chapter indicate that CNV frequency analysis and discriminant analysis provide an effective method for differentiating between HD, PD and schizophrenic patients and normal subjects.

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Chapter 8 Identification of Schizophrenic, Parkinson's Disease and Huntington's Disease Patients by Using the CNV Time Domain Features in Neural Networks

The brain contains a large number of information processing elements, called neurons. Neural networks (artificial neural networks) are computer models that simulate the functioning of the brain in a very simplified manner. Neural networks are capable of generalisation and, because of their highly parallel structure, they can offer real-time solutions to complex optimisation problems. Furthermore, the application of neural networks requires less restrictive assumptions about the statistical nature of the data (ie. the distribution of discriminatory variables) and they have been effective in cases involving noisy signals.

It was decided to use neural networks because it was considered that they might provide a less complex method (compared to the method described in chapter 7) of identifying the patients. Neural networks use either supervised or unsupervised learning algorithms. In this study neural networks with supervised learning algorithms (ie. multilayer perceptron networks) were used and therefore the discussion provided in this chapter relates to the supervised learning neural networks. Supervised learning neural networks operate in two modes. In the "learning" (or "training") mode several input patterns and their corresponding output values are compared with the desired output values and the neural network parameters are adapted to cause the actual outputs to approximate the desired outputs. In the "test" (or "use") mode the neural network is used to classify patterns where their classes are not known (ie. the test patterns). The test patterns must belong to the classes included during the training phase.

Neural networks have been widely used for pattern recognition, for example, Gorman and Sejnowski [1988] successfully used neural networks to classify sonar return signals from two undersea targets.

There is a rising interest in the use of neural networks in the medical field [McDonald and McDonald, 1991]. Bounds and Lloyd [1988] used neural networks to analyse data concerned with four classes of back pain. Neural networks were trained on 25 examples from each class of pain. The overall performance of the neural networks on the test pattern example set, which contained a similar number of examples as the training set, was 80%. Schizas et al. [1989] used neural networks for classification of electromyographic signals. They selected the amplitude, area, average power and duration of the signals as the features. The neural network success rate in correctly classifying the test patterns was about 60%. They suggested an improved method of selecting the features could increase the success rate. An attempt was made to identify high risk cardiac cases from "no-risk" cases by Hart and Wyatt [1989]. They could not accurately differentiate the test cases. The complexity of the problem and lack of sufficient examples from the different cases were believed to have contributed to the low success rate [Hart, 1990]. Yoon et al. [1989] used a 3-layer neural network to aid the differentiation of 10 skin diseases. They represented the symptoms related to each skin disease by 18 variables and achieved an overall success rate of 70% in the test mode. Several attempts have been made to classify EEG patterns using neural networks [Choi et al., 1991] [Jarratt, 1991]. These results seem to be promising.

In this chapter a brief account of neural network theory is provided, a time domain feature extraction method suitable for the CNV is described and the results on patient identification obtained following the processing of the CNV waveforms of schizophrenic, Parkinson's disease and Huntington's disease patients and their normal control subjects by neural networks are discussed.

8.1 Theoretical Analysis of Neural Networks

Figure (8.1) shows a node (neuron, or unit) used as a building block for a neural network. The input vector x brings the information from external sources. The amount of influence the inputs exert on a node is controlled by the weight vector w. The values of the inputs and their corresponding weights are combined using a combining function. A commonly used combining function is the weighted sum of the inputs. The procedure for this function is to multiply every input with its associated weight and then sum the results. The transfer function (or threshold function) interprets the combining function output. A traditionally used transfer function is the sigmoid function shown in Figure (8.2). The sigmoid function is defined as,

$$f(x) = \frac{1}{1 + \exp(-(x+\Theta_j)/\Theta_o)} \qquad \ldots(8.1)$$

Θ_j is known as the bias or the threshold value and its effect is to shift the transfer function to the left or right along the horizontal axis. The value of the constant Θ_o determines the slope of the sigmoid as shown in Figure (8.2).

A single node on its own has little processing power. The capabilities of neural networks lie in several nodes being interconnected to form structures such as the one shown in Figure (8.3). The neural network shown in Figure (8.3) has an input layer, an output layer and a layer not connected directly to the input or the output, and so-called the "hidden layer". The input layer distributes the input data to the hidden layer. The hidden layer (there may be more than one hidden layer) and the output layer are responsible for processing the data and presenting the results to the output.

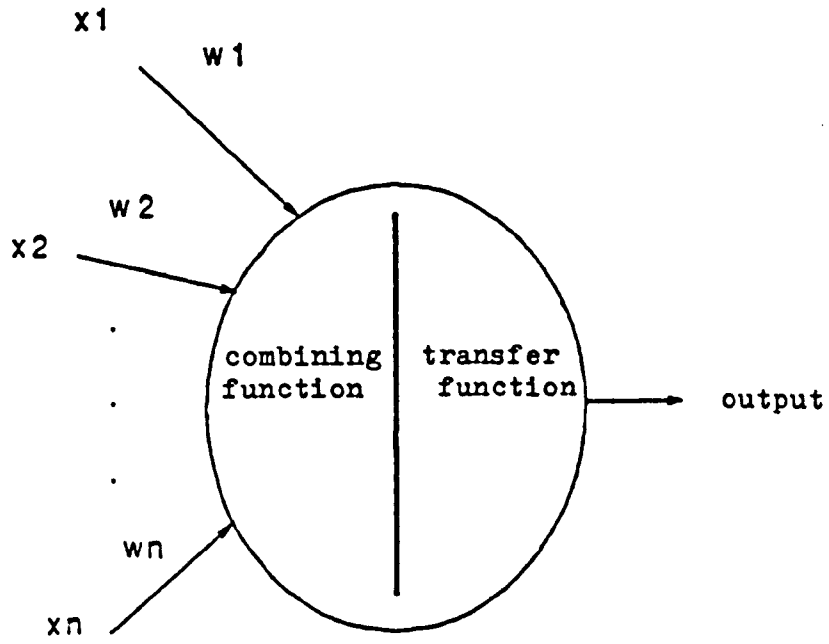

Figure 8.1 A node in a neural network.

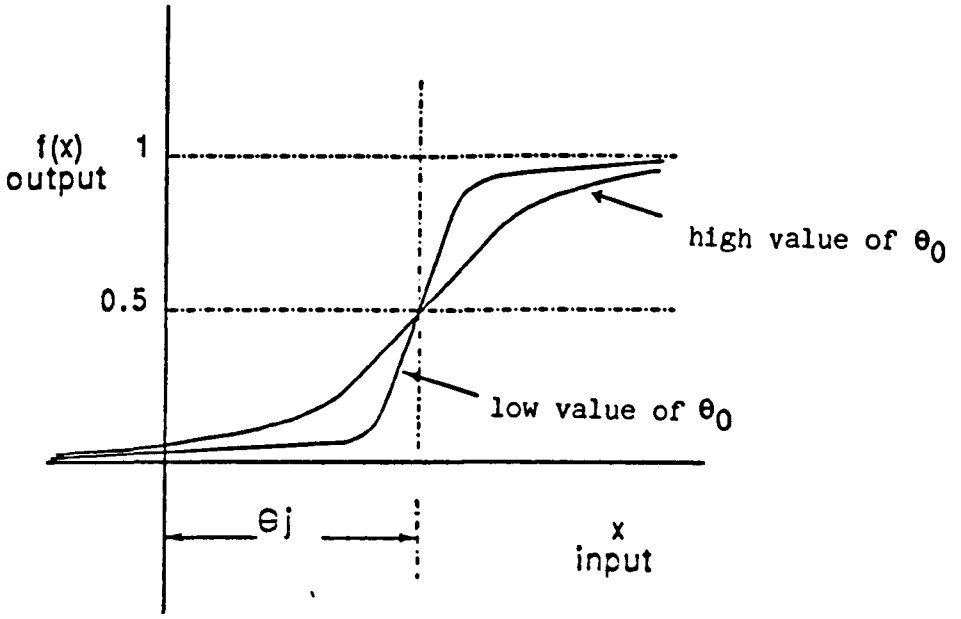

Figure 8.2 A sigmoid transfer function.

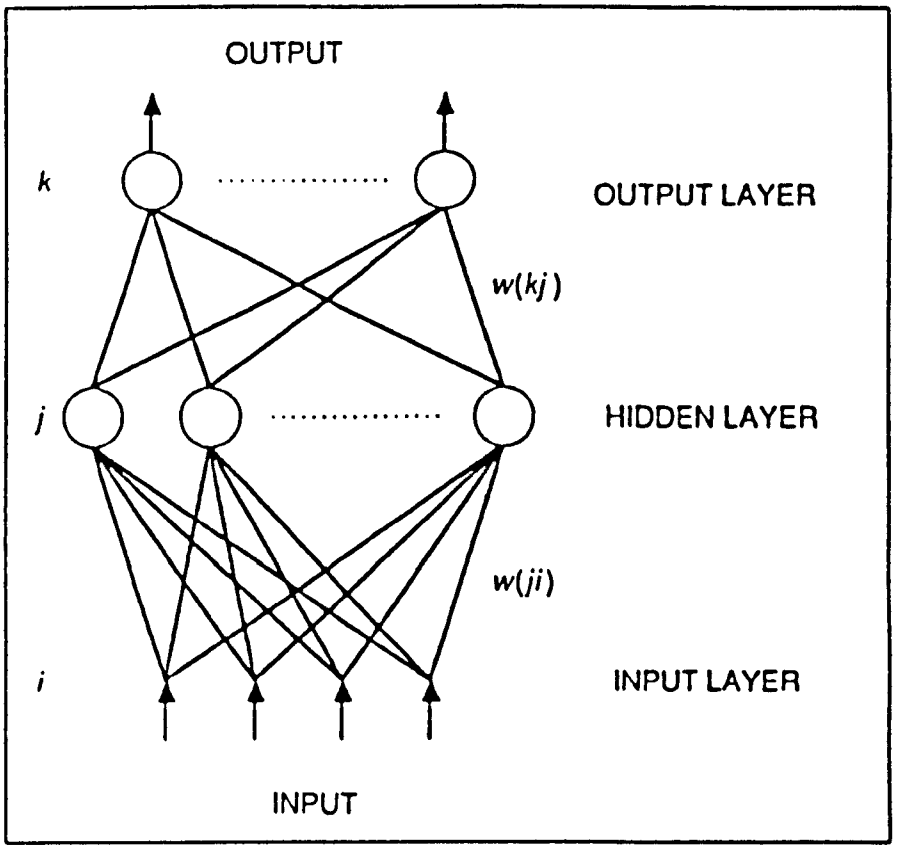

Figure 8.3 A multilayer neural network.

If o_i is the output of a node in the layer i then the input to a node in the layer j, (in_j) is,

$$in_j = \Sigma\, w_{ji} o_i \qquad \ldots(8.2)$$

where w_{ji} is the weight associated with the connection from a node in the layer i to a node in the layer j. The output of a node in the layer j, (o_j) is a function of the node's input. Using a sigmoid as the transfer function,

$$o_j = f(in_j) \qquad \ldots(8.3)$$

ie.
$$o_j = \frac{1}{1 + \exp(-(in_j + \theta_j)/\theta_o)} \qquad \ldots(8.4)$$

The input to a node in the layer k, (in_k) is,

$$in_k = \Sigma\, w_{kj} o_j \qquad \ldots(8.5)$$

and its output (o_k), using a sigmoid transfer function is,

$$o_k = f(in_k) \qquad \ldots(8.6)$$

ie.
$$o_k = \frac{1}{1 + \exp(-(in_k + \theta_k)/\theta_o)} \qquad \ldots(8.7)$$

If a node in the output layer, for a pattern p, has an output o_{pk}, and its desired output is t_{pk}, then the sum of the squared errors (error function) will be,

$$E_p = \frac{1}{2} \sum_k (t_{pk} - o_{pk})^2 \qquad \ldots(8.8)$$

The factor ½ simplifies the mathematics during the succeeding stages of the analysis.

The weights and biases need to be adjusted in order to reduce the error function E_p. A widely used method of "learning" the weights and the biases is the generalised delta rule sometimes referred to as the backpropagation rule [Rumelhart et al., 1986]. Initially the weights and biases are set to small random numbers. This is necessary for correct operation of the backpropagation rule [Rumelhart et al., 1986]. Then the weights and biases are adjusted so that the error E_p is reduced as rapidly as possible. As a detailed analysis of the backpropagation rule can be found in several publications such as Rumelhart et al. [1987], Beale and Jackson [1990] and Aleksander and Morton [1990], derivation of the backpropagation rule is not given.

Using the backpropagation rule, the change in the weights in the $(n+1)^{th}$ step for the connections in the output layer is given by,

$$\blacktriangle_p w_{kj}(n+1) = \beta \delta_{pk} o_{pj} + \alpha \blacktriangle_p w_{kj}(n) \qquad ...(8.9)$$

where β is the learning rate. A large β produces a rapid learning but can also result in oscillation. δ_{pk} is,

$$\delta_{pk} = (t_{pk} - o_{pk})\, o_{pk}\, (1 - o_{pk}) \qquad ...(8.10)$$

The proportionality constant, α is called the momentum. The value of $\blacktriangle_p w_{kj}(n)$ is initially zero.

The change in the weights in the $(n+1)^{th}$ step for the connections in the hidden layer is given by,

$$\blacktriangle_p w_{ji}(n+1) = \beta \delta_{pj} o_{pi} + \alpha \blacktriangle_p w_{ji}(n) \qquad ...(8.11)$$

where $$\delta_{pj} = o_{pj} (1 - o_{pj}) \sum_{k} \delta_{pk} w_{kj} \quad ...(8.12)$$

Initially the value of $\alpha \Delta_p w_{ji}(n)$ is equal to zero. The bias values are treated as incoming weights from a unit whose output is always 1 and they are adjusted in the same manner as the weight values.

To summarise, neural network learning phase involves:

i) Setting all the weight and bias values to small random numbers.
ii) Reading in a training pattern and its associated desired value.
iii) Calculating the outputs of the nodes in the hidden and the output layers using (8.4) and (8.7).
iv) Adjusting the weight and bias values using (8.9) and (8.11).
v) Repeating the process (ii) to (iv) for the remaining patterns in the training file.

The learning process is repeated until the neural network is capable of accurately identifying the test patterns (ie. until it has generalised).

8.2 Time Domain Feature Extraction Method Applied to the CNV

In chapter 7, a method of feature extraction based on data transformation into the frequency domain was described. In order to reduce the complexity of the analysis and to reduce the processing time, it was decided to investigate whether it was possible to obtain the discriminatory features by analysing the CNV in the time domain.

Shiavi and Bourne [1986] described a series of parameters which could be used to represent electrophysiological signals. These included amplitude, slope and duration. However application of these parameters to the CNV could not provide sufficiently sensitive measures for identifying the patients. This was because

although the parameters provided a quantitative measure for the CNV, they did not accurately describe the shape of the CNV which was also believed to be important. A method applied to carotid pulse-wave (CPW) by Stockman et al. [1976] involved identifying the points on the waveform in such a way that they provided a reasonably complete description of the fundamental activity of the signal in the time domain.

The method adopted, like the method used by Stockman et al. [1976], involved obtaining a set of time domain points which could best represent the section of the CNV relevant in the patient identification. Eight CNV trials not grossly contaminated by ocular artefact were used per subject. The CNV trials were subjected to a preprocessing procedure which carried out mean level removal, baseline correction, digital low-pass filtering and ocular artefact removal. These steps were discussed in chapter 6 and they were carried out using a Turbo Pascal program called PROC.PAS (a listing of this program is included in Appendix C). The CNV trials were then averaged. The CNV response tends to follow a constant profile. By contrast the background EEG activity could be considered to have a randomly distributed amplitude about zero. The effect of averaging is to reduce the unwanted background EEG (ie. noise) by a factor proportional to $\sqrt{n}$, where n is the number of trials averaged [Binnie, 1982]. The reduction in the number of CNV trials (compared to the method described in chapter 7) reduced the data recording and processing times. It also reduced the distortion due to the inter-trial CNV variability. It should be noted that the successive CNV trials are not 100% identical. The variations are caused by factors such as changes in patients' attention during the data recording and give rise to the inter-trial variability [Binnie et al. 1982]. The digital low-pass filter cut-off frequency was reconsidered (this was 30Hz for the method described in chapter 7) to take into account the changes in the method of feature extraction and

therefore it was set to 7.5Hz. The frequency response of this filter is shown in chapter 6. Ruchkin [1988] reported that the details of the CNV were preserved when the cut-off frequency of the digital low-pass filter was 5.5Hz. Therefore this reduction in the filter's cut-off frequency was acceptable.

Seventeen CNV features were used as inputs to the neural networks. Sixteen features were extracted from a section 512ms prior to the imperative-stimulus in the preprocessed and averaged CNV waveform (listing of the program used for this purpose is given in Appendix (D)). A moving average window, with a window size of four samples (corresponding to 32ms), was applied to this section. This averaged every four consecutive sample values producing sixteen CNV features (or variables). Figure (8.4) shows the effect of this process on the CNV section used in the analysis. This method was suitable as it further reduced the effect of the almost random background EEG and it also closely represented the CNV section of interest. In the majority of normal subjects the CNV returns to the baseline rapidly following the onset of the imperative-stimulus and the subject's response to that stimulus. It has been shown, however, that in 75% of schizophrenic patients and 37% of neurotic patients the CNV takes more than 2 seconds to return to the baseline [Dubrovsky and Dongier, 1976]. To include this effect, a seventeenth feature was obtained. This feature was the time difference between the onset of the imperative-stimulus and the point where the CNV returned to its baseline. This time period is shown in Figure (8.5). It should be noted that the PINV was measured manually by determining the point where the CNV trend crossed the baseline.

8.3 Procedure for Obtaining the Results

Twenty schizophrenic patients, sixteen Parkinson's disease (PD) patients, eleven Huntington's disease (HD) patients and their normal control subjects were included in the analysis (refer to Tables (8.1)-(8.3) for more details).

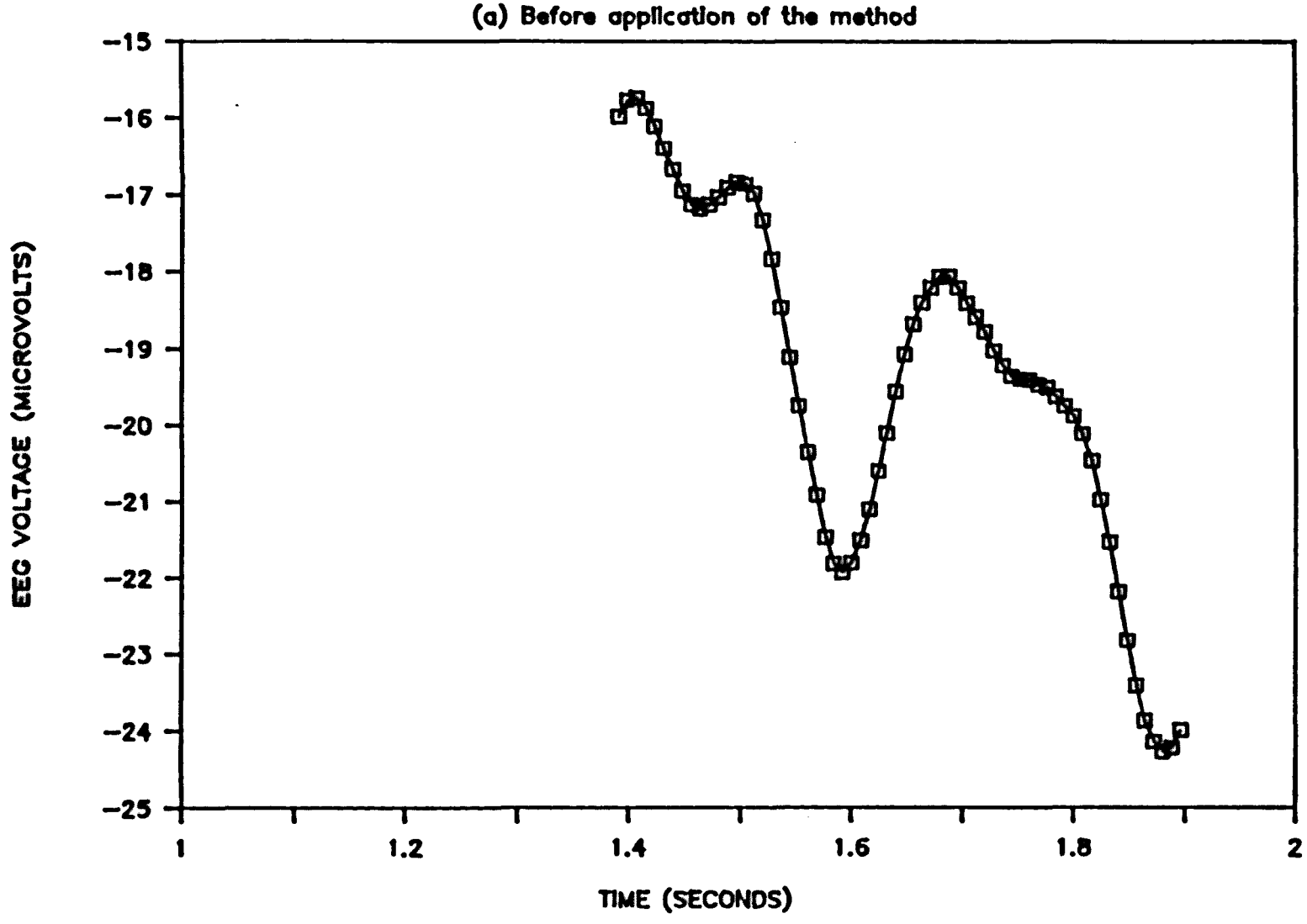

Figure 8.4 The effect of moving average window during CNV feature extraction. (a) before application of the method.

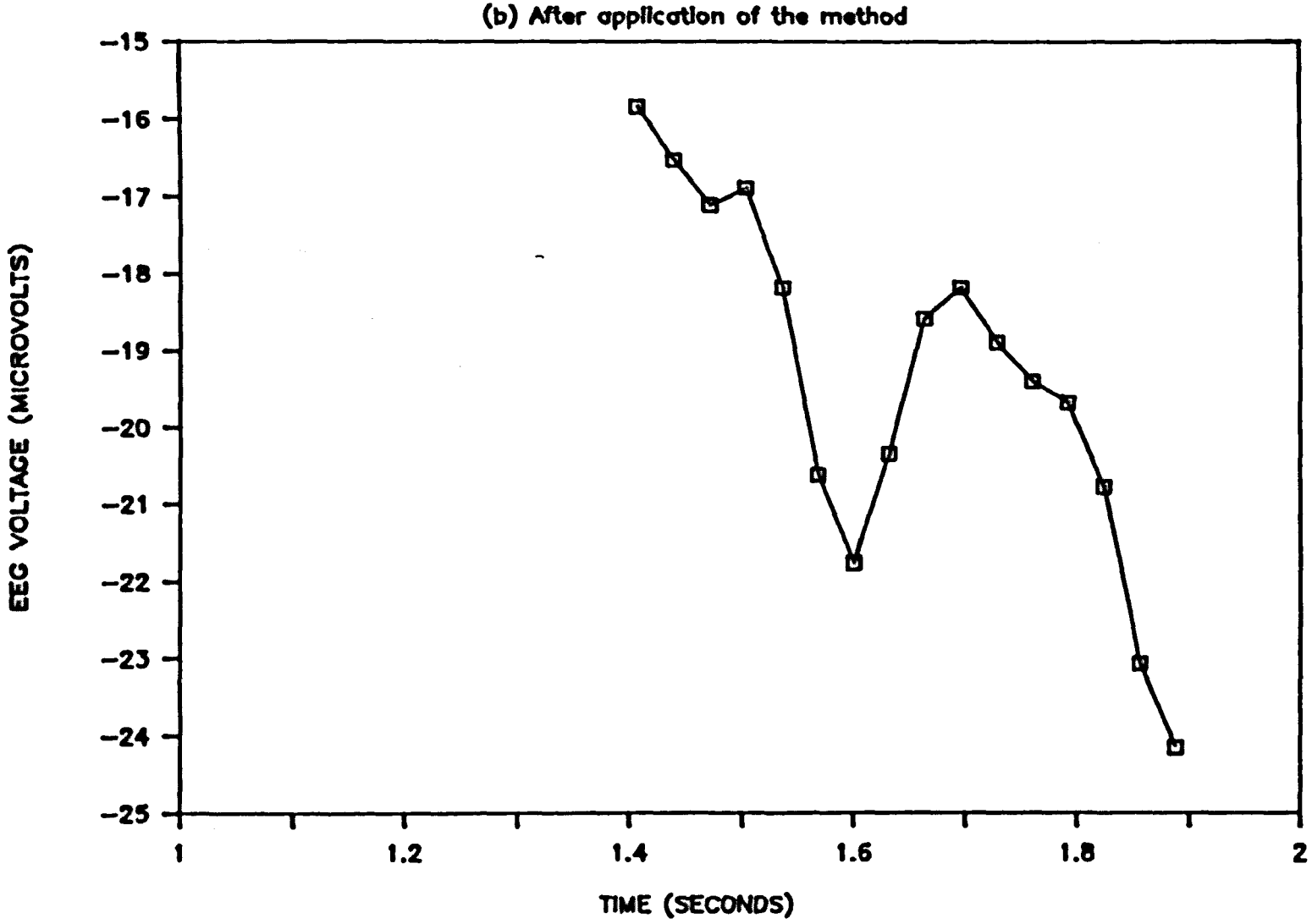

Figure 8.4 The effect of moving average window during CNV feature extraction. (b) after the application of the method.

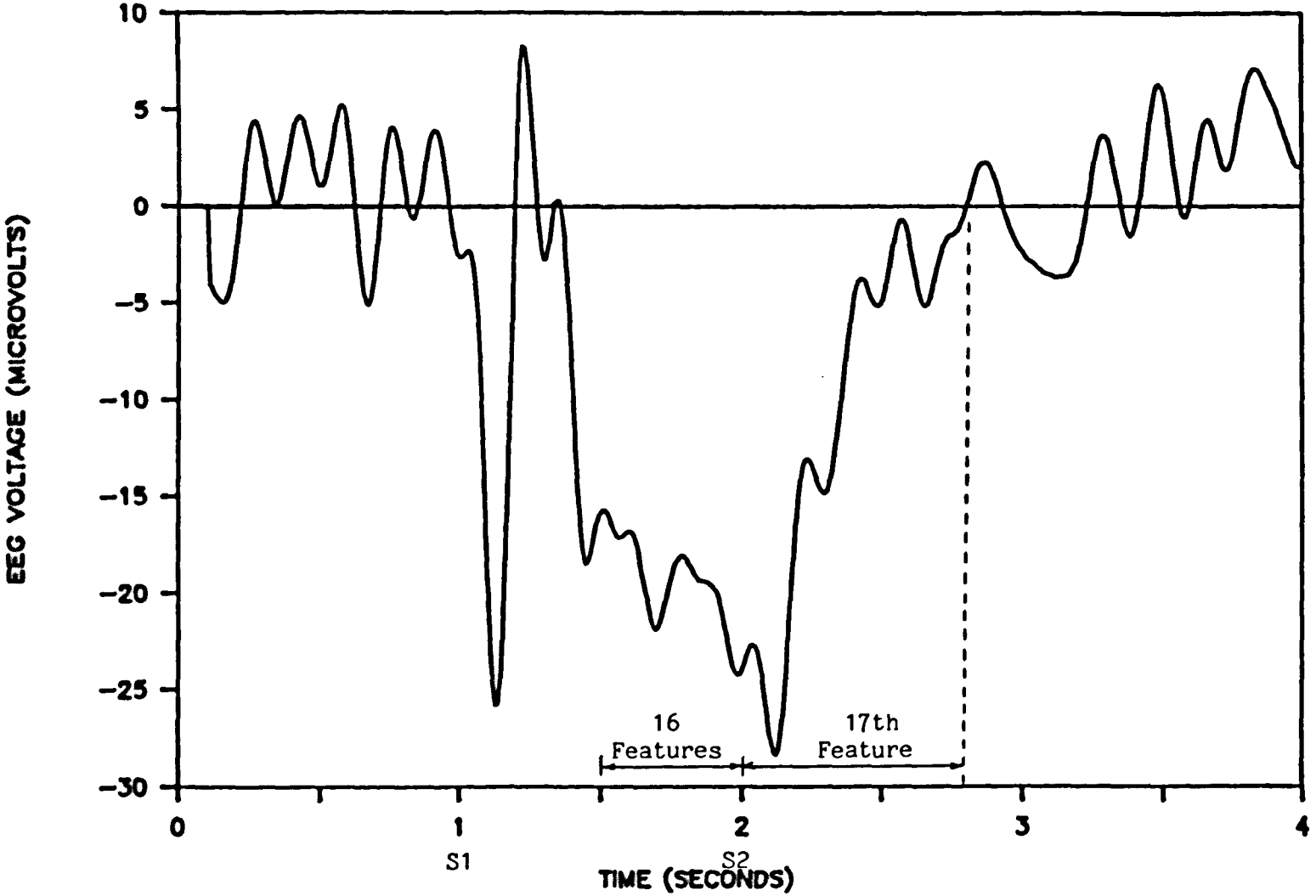

Figure 8.5 The CNV sections from which the discriminatory features were obtained.

Table (8.1) Details of schizophrenic patients and their normal control subjects.

Parameters		Subjects' Categories	
		Schizophrenic Patients	Control Subjects
number of subjects	total	20 (15 male)	20 (15 male)
	on drug	18	0
age	mean	33.60	39.50
	STD	12.22	13.66
	range	20 to 68	22 to 75

Table (8.2) Details of Parkinson's disease patients and their normal control subjects.

Parameters		Subjects' Categories	
		Parkinson's Disease	Control Subjects
number of subjects	total	16 (10 male)	16 (10 male)
	on drug	12	0
age	mean	63.63	50.81
	STD	9.68	11.16
	range	42 to 80	35 to 75

Table (8.3) Details of Huntington's disease patients and their normal control subjects.

Parameters		Subjects' Categories	
		Huntington's Disease	Control Subjects
number of subjects	total	11 (6 male)	11 (6 male)
	on drug	5	0
age	mean	53.73	50.09
	STD	10.97	10.53
	range	39 to 77	40 to 73

Seventeen features were obtained from each preprocessed averaged CNV waveform as described in section (8.2). The selected features for the patients in each category and their normal control subjects were normalised between 0 and 1. The normalisation of the features was desirable as otherwise during the implementation of neural networks numbers with unacceptably large magnitudes could have resulted. To normalise the selected features for the patients in a category such as schizophrenic patients and their normal control subjects, a computer program read the 16 features selected from the inter-stimulus intervals of the CNVs of these subjects. The maximum and minimum values of these features were identified. Then the normalisation of the features selected from the inter-stimulus interval (ISI) was achieved using,

$$NF_{isi} = \frac{F_{isi}}{|MIN_{isi}|+|MAX_{isi}|} + \frac{|MIN_{isi}|}{|MIN_{isi}|+|MAX_{isi}|} \qquad \ldots(8.13)$$

where NF_{isi} is the normalised feature,
F_{isi} is the feature not normalised,
MIN_{isi} is minimum value of the features,
MAX_{isi} is maximum value of the features.

In order to normalise the 17th feature, the maximum and minimum values of the PINV for the patients in each category and their normal control subjects were obtained. Then these features were normalised by,

$$NF_{pinv} = \frac{F_{pinv} - MIN_{pinv}}{MAX_{pinv} - MIN_{pinv}} \qquad \ldots(8.14)$$

where NF_{pinv} is normalised feature,
F_{pinv} is not normalised feature,
MIN_{pinv} is minimum value of the PINV,
MAX_{pinv} is maximum value of the PINV.

The patients in each category and their normal control subjects were divided into two groups in such away that an individual in the first group was age and sex matched with another individual in the second group. Two files were formed for each patient category. The first file contained the normalised CNV features of half the patients from a patient category and their normal control subjects and was used to train the neural networks. The order of subjects' entry in the training file was random, ie. a normal subject was randomly followed by either another normal or a patient. The second file contained the normalised CNV features of the remaining patients from that category and their normal control subjects and was used to evaluate the effectiveness of the neural networks in the test mode. This process was repeated for the two other patient categories.

A commercially available package called NeuralWorks, was used to implement the multilayer neural networks. The manual accompanying it provided a comprehensive explanation of how to use that software [NeuralWorks Manual, 1988]. The structure of the neural networks used is described in section (8.1). The NeuralWorks package permitted inclusion of up to two hidden layers. The number of nodes in the input layer was always 17, ie. one node per CNV feature. As the aim was to distinguish between the patients of a category and normal

subjects, one output node was sufficient. During the training this node took a value of 1 to represent normal subjects and 0 for the patients. The standard backpropagation method referred to in section (8.1) was used for the learning algorithm. A heuristic method is generally used to determine the number the nodes in the hidden layer(s). If sufficient nodes are not included in the hidden layer(s), the learning process will be hindered. Too many nodes in the hidden layer(s), however can cause a degradation of the generalisation capability of the neural network [Bhagat, 1990]. The classification threshold level was 0.5. Therefore if the outputs of neural networks following training were between 0.5 and 1.0 the individuals were considered "normal", and if the outputs were between 0 and 0.5 the individuals were considered "patient".

The type of the transfer function used was sigmoidal (as shown in Figure (8.2)). The weights for the connections were initially randomised to lie between -0.1 and 0.1. The NeuralWorks software recommended that the value of Θ_o to be 1, the value of α to be 0.6 and the value of ß to be 0.9 (see NeuralWorks Manual [1988] for detail). It was decided to keep these parameters to the recommended values and change them if it became necessary. A network with 17 units in the input layer, 10 units in the first hidden layer, 5 units in the second hidden layer and 1 unit in the output layer was set up by following the instructions in NeuralWorks manual. The neural network was initially trained on 10 schizophrenic patients and their normal control subjects and tested the remaining 10 schizophrenic patients and their normal control subjects. The output of the neural network for each subject after 3000, 6000, 9000 and 12000 iterations were examined. This indicated that the neural network performed best (ie. least error) after 12000 iterations. It was then decided to keep the number of iterations to 12000 and investigate the effect of changing the number of units in the hidden layer(s). In the case HD patients and their normal control subjects, as in schizophrenic patients the number

of iterations was kept to 12000 and the effect of changing the number of units in the hidden layer(s) was investigated. For PD patients and their normal control subjects, the outputs of the neural networks after 12000, 20000 and 24000 iteration were analysed.

Tables (8.4)-(8.10) show the outputs of neural networks for the patients and their normal control subjects for different numbers of units in the hidden layer(s). The performance of neural networks in differentiating between patients is summarised in Tables (8.11)-(8.13).

Table (8.4) Neural Network outputs for schizophrenic patients and their normal control subjects. Number of units in the hidden layers 20 and 20, and 30 and 20.

Training				Test		
Network Structure	Subject Number	Desired Value	Network Output	Subject Number	Desired Value	Network Output
17-20-20-1	1	0	0.00507	21	0	0.00401
	2	0	0.00524	22	0	0.00153
	3	1	1.00000	23	0	1.00000
	4	0	0.00795	24	0	0.00143
	5	1	1.00000	25	0	0.21516
	6	0	0.03564	26	0	0.01292
	7	1	1.00000	27	0	0.00171
	8	0	0.00445	28	0	0.00176
	9	0	0.00286	29	0	0.00541
	10	1	1.00000	30	0	0.00161
	11	0	0.00427	31	1	1.00000
	12	1	0.97588	32	1	1.00000
	13	0	0.00147	33	1	1.00000
	14	1	0.99999	34	1	1.00000
	15	0	0.00210	35	1	1.00000
	16	1	1.00000	36	1	1.00000
	17	1	1.00000	37	1	0.99998
	18	0	0.00905	38	1	0.99539
	19	1	1.00000	39	1	1.00000
	20	1	0.99542	40	1	1.00000
17-30-20-1	1	0	0.00494	21	0	0.00399
	2	0	0.00509	22	0	0.00183
	3	1	1.00000	23	0	1.00000
	4	0	0.00717	24	0	0.00173
	5	1	1.00000	25	0	0.18652
	6	0	0.03444	26	0	0.01116
	7	1	1.00000	27	0	0.00200
	8	0	0.00451	28	0	0.00204
	9	0	0.00302	29	0	0.00543
	10	1	1.00000	30	0	0.00190
	11	0	0.00439	31	1	1.00000
	12	1	0.97847	32	1	1.00000
	13	0	0.00177	33	1	1.00000
	14	1	0.99999	34	1	1.00000
	15	0	0.00234	35	1	1.00000
	16	1	1.00000	36	1	1.00000
	17	1	1.00000	37	1	1.00000
	18	0	0.00776	38	1	0.99675
	19	1	1.00000	39	1	1.00000
	20	1	0.99545	40	1	1.00000

Table (8.5) Neural Network outputs for schizophrenic patients nd their normal control subjects. Number of units in the hidden 10 and 5, and 8 and 8.

Training				Test		
Network Structure	Subject Number	Desired Value	Network Output	Subject Number	Desired Value	Network Output
17-10-5-1	1	0	0.00548	21	0	0.00478
	2	0	0.00566	22	0	0.00380
	3	1	0.99998	23	0	0.99994
	4	0	0.00886	24	0	0.00375
	5	1	0.99997	25	0	0.11894
	6	0	0.03153	26	0	0.01130
	7	1	0.99999	27	0	0.00388
	8	0	0.00517	28	0	0.00392
	9	0	0.00459	29	0	0.00551
	10	1	0.99994	30	0	0.00383
	11	0	0.00568	31	1	0.99997
	12	1	0.97790	32	1	0.99998
	13	0	0.00377	33	1	0.99998
	14	1	0.99991	34	1	0.99996
	15	0	0.00404	35	1	0.99994
	16	1	0.99998	36	1	0.99999
	17	1	0.99997	37	1	0.99984
	18	0	0.00724	38	1	0.99700
	19	1	0.99996	39	1	0.99996
	20	1	0.99766	40	1	0.99998
17-8-8-1	1	0	0.00316	21	0	0.00299
	2	0	0.00332	22	0	0.00203
	3	1	1.00000	23	0	0.99999
	4	0	0.00596	24	0	0.00198
	5	1	1.00000	25	0	0.10060
	6	0	0.02255	26	0	0.00694
	7	1	1.00000	27	0	0.00207
	8	0	0.00291	28	0	0.00210
	9	0	0.00254	29	0	0.00329
	10	1	1.00000	30	0	0.00204
	11	0	0.00371	31	1	1.00000
	12	1	0.98428	32	1	1.00000
	13	0	0.00199	33	1	1.00000
	14	1	0.99999	34	1	1.00000
	15	0	0.00218	35	1	0.99999
	16	1	1.00000	36	1	1.00000
	17	1	1.00000	37	1	0.99997
	18	0	0.00374	38	1	0.99842
	19	1	1.00000	39	1	1.00000
	20	1	0.99809	40	1	1.00000

Table (8.6) Neural Network outputs for schizophrenic patients and their normal control subjects. Number of units in the hidden layer 50 and 40.

Training				Test		
Network Structure	Subject Number	Desired Value	Network Output	Subject Number	Desired Value	Network Output
17-50-1	1	0	0.00191	21	0	0.00097
	2	0	0.00149	22	0	0.00000
	3	1	1.00000	23	0	1.00000
	4	0	0.00354	24	0	0.00000
	5	1	1.00000	25	0	0.35165
	6	0	0.02775	26	0	0.01580
	7	1	1.00000	27	0	0.00001
	8	0	0.00184	28	0	0.00001
	9	0	0.00072	29	0	0.00858
	10	1	0.99997	30	0	0.00000
	11	0	0.00180	31	1	1.00000
	12	1	0.97361	32	1	1.00000
	13	0	0.00000	33	1	1.00000
	14	1	0.99985	34	1	1.00000
	15	0	0.00007	35	1	0.99998
	16	1	1.00000	36	1	1.00000
	17	1	1.00000	37	1	0.99994
	18	0	0.01163	38	1	0.98862
	19	1	1.00000	39	1	1.00000
	20	1	0.99050	40	1	1.00000
17-40-1	1	0	0.00197	21	0	0.00136
	2	0	0.00169	22	0	0.00001
	3	1	1.00000	23	0	1.00000
	4	0	0.00369	24	0	0.00000
	5	1	1.00000	25	0	0.35503
	6	0	0.02903	26	0	0.01541
	7	1	1.00000	27	0	0.00001
	8	0	0.00194	28	0	0.00002
	9	0	0.00064	29	0	0.00939
	10	1	0.99997	30	0	0.00000
	11	0	0.00237	31	1	1.00000
	12	1	0.97303	32	1	1.00000
	13	0	0.00000	33	1	1.00000
	14	1	0.99982	34	1	1.00000
	15	0	0.00009	35	1	0.99998
	16	1	1.00000	36	1	1.00000
	17	1	1.00000	37	1	0.99994
	18	0	0.01188	38	1	0.98874
	19	1	1.00000	39	1	1.00000
	20	1	0.99087	40	1	1.00000

Table (8.7) Neural Network outputs for Parkinson's Disease patients and their normal control subjects. Number of units in the hidden layers 40 and 60.

Training				Test		
Network Structure	Subject Number	Desired Value	Network Output	Subject Number	Desired Value	Network Output
17-40-1	1	0	0.01831	17	0	0.00073
	2	0	0.05613	18	0	0.00131
	3	1	0.99984	19	0	0.00162
	4	0	0.00016	20	0	0.35689
	5	1	0.96716	21	0	0.00000
	6	0	0.00000	22	0	0.00000
	7	0	0.04357	23	0	0.25433
	8	1	0.99950	24	0	0.04962
	9	0	0.01580	25	1	1.00000
	10	1	1.00000	26	1	1.00000
	11	0	0.00010	27	1	0.99919
	12	1	0.97249	28	1	0.99999
	13	1	0.97540	29	1	1.00000
	14	0	0.00016	30	1	1.00000
	15	1	0.97204	31	1	0.09948
	16	1	1.00000	32	1	1.00000
17-60-1	1	0	0.07926	17	0	0.05851
	2	0	0.61806	18	0	0.27015
	3	1	0.99962	19	0	0.08742
	4	0	0.17059	20	0	0.61578
	5	1	0.96600	21	0	0.00001
	6	0	0.00018	22	0	0.00041
	7	0	0.47536	23	0	0.65005
	8	1	0.99673	24	0	0.02517
	9	0	0.53862	24	1	1.00000
	10	1	1.00000	26	1	0.99999
	11	0	0.05447	27	1	0.99881
	12	1	0.96628	28	1	0.99991
	13	1	0.94782	29	1	1.00000
	14	0	0.03650	30	1	1.00000
	15	1	0.97175	31	1	0.62900
	16	1	0.99992	32	1	0.99997

Table (8.8) Neural Network outputs for Parkinson's Disease patients and their normal control subjects. Number of units in the hidden layers 20 and 20, 25 and 25.

Training				Test		
Network Structure	Subject Number	Desired Value	Network Output	Subject Number	Desired Value	Network Output
17-20-20-1	1	0	0.00250	17	0	0.00241
	2	0	1.00000	18	0	0.00134
	3	1	1.00000	19	0	0.95752
	4	0	0.00234	20	0	0.12137
	5	1	1.00000	21	0	0.00066
	6	0	0.00067	22	0	0.00085
	7	0	0.00908	23	0	1.00000
	8	1	0.99997	24	0	0.00224
	9	0	0.02473	25	1	1.00000
	10	1	1.00000	26	1	1.00000
	11	0	0.00070	27	1	1.00000
	12	1	0.99919	28	1	1.00000
	13	1	0.98142	29	1	0.99983
	14	0	0.00070	30	1	1.00000
	15	1	0.99983	31	1	1.00000
	16	1	0.99957	32	1	1.00000
17-25-25-1	1	0	0.00634	17	0	0.00413
	2	0	1.00000	18	0	0.00292
	3	1	1.00000	19	0	0.87640
	4	0	0.00455	20	0	0.31919
	5	1	1.00000	21	0	0.00157
	6	0	0.00159	22	0	0.00201
	7	0	0.00888	23	0	1.00000
	8	1	0.99995	24	0	0.00755
	9	0	0.03521	25	1	1.00000
	10	1	1.00000	26	1	1.00000
	11	0	0.00165	27	1	1.00000
	12	1	0.99820	28	1	1.00000
	13	1	0.97569	29	1	0.99993
	14	0	0.00164	30	1	1.00000
	15	1	0.99940	31	1	1.00000
	16	1	0.99929	32	1	1.00000

Table (8.9) Neural Network outputs for Parkinson's Disease patients and their normal control subjects. Number of units in the hidden layers 10 and 10, and 20 and 10.

Training				Test		
Network Structure	Subject Number	Desired Value	Network Output	Subject Number	Desired Value	Network Output
17-10-10-1	1	0	0.00592	17	0	0.00475
	2	0	0.99997	18	0	0.00343
	3	1	1.00000	19	0	0.90638
	4	0	0.00485	20	0	0.23380
	5	1	0.99995	21	0	0.00255
	6	0	0.00256	22	0	0.00281
	7	0	0.01132	23	0	0.99999
	8	1	0.99985	24	0	0.00566
	9	0	0.03728	25	1	1.00000
	10	1	1.00000	26	1	0.99999
	11	0	0.00260	27	1	1.00000
	12	1	0.99862	28	1	1.00000
	13	1	0.97329	29	1	0.99972
	14	0	0.00260	30	1	1.00000
	15	1	0.99945	31	1	1.00000
	16	1	0.99925	32	1	1.00000
17-20-10-1	1	0	0.00716	17	0	0.00492
	2	0	0.99999	18	0	0.00345
	3	1	1.00000	19	0	0.91211
	4	0	0.00579	20	0	0.20454
	5	1	0.99996	21	0	0.00243
	6	0	0.00244	22	0	0.00273
	7	0	0.01216	23	0	1.00000
	8	1	0.99983	24	0	0.00538
	9	0	0.03823	25	1	1.00000
	10	1	1.00000	26	1	1.00000
	11	0	0.00249	27	1	1.00000
	12	1	0.99887	28	1	1.00000
	13	1	0.97313	29	1	0.99926
	14	0	0.00248	30	1	1.00000
	15	1	0.99961	31	1	1.00000
	16	1	0.99885	32	1	1.00000

Table (8.10) Neural Network outputs for Huntington's Disease patients and their normal control subjects. Number of units in the hidden layers 20 and 20, 25 and 25, and 10 and 10.

Training				Test		
Network Structure	Subject Number	Desired Value	Network Output	Subject Number	Desired Value	Network Output
17-20-20-1	1	0	0.01732	13	0	0.05641
	2	1	0.99886	14	0	0.24174
	3	0	0.00168	15	0	0.00088
	4	1	0.98986	16	0	0.24912
	5	0	0.01301	17	0	0.22759
	6	0	0.00133	18	1	1.00000
	7	1	0.98934	19	1	0.79412
	8	0	0.00358	20	1	0.99975
	9	1	0.99968	21	1	0.99950
	10	1	0.99164	22	1	0.99899
	11	0	0.00481			
	12	1	0.99969			
17-25-25-1	1	0	0.01725	13	0	0.05661
	2	1	0.99898	14	0	0.25233
	3	0	0.00162	15	0	0.00078
	4	1	0.98987	16	0	0.26518
	5	0	0.01302	17	0	0.22297
	6	0	0.00122	17	1	1.00000
	7	1	0.98959	19	1	0.76972
	8	0	0.00343	20	1	0.99979
	9	1	0.99971	21	1	0.99957
	10	1	0.99191	22	1	0.99902
	11	0	0.00455			
	12	1	0.99972			
17-10-10-1	1	0	0.01625	13	0	0.05088
	2	1	0.99875	14	0	0.23384
	3	0	0.00231	15	0	0.00155
	4	1	0.99085	16	0	0.24379
	5	0	0.01245	17	0	0.21647
	6	0	0.00197	18	1	0.99999
	7	1	0.99057	19	1	0.81479
	8	0	0.00400	20	1	0.99968
	9	1	0.99960	21	1	0.99939
	10	1	0.99256	22	1	0.99897
	11	0	0.00512			
	12	1	0.99961			

Table (8.11) Summary of patients' differentiation success rate for schizophrenic patients and their normal control subjects.

Number Of Units	Training Mode		Test Mode		Number Of Iterations
	Patients	Controls	Patients	Controls	
17-20-20-1	100%	100%	90%	100%	12000
17-30-20-1	100%	100%	90%	100%	12000
17-50-1	100%	100%	90%	100%	12000
17-10-5-1	100%	100%	90%	100%	12000
17-8-8-1	100%	100%	90%	100%	12000
17-40-1	100%	100%	90%	100%	12000

Table (8.12) Summary of patients' differentiation success rate for Parkinson's disease patients and their normal control subjects.

Number Of Units	Training Mode		Test Mode		Number Of Iterations
	Patients	Controls	Patients	Controls	
17-20-20-1	87.5%	100%	75%	100%	20000
17-25-25-1	87.5%	100%	75%	100%	12000
17-10-10-1	87.5%	100%	75%	100%	12000
17-20-10-1	87.5%	100%	75%	100%	12000
17-40-1	100%	100%	100%	87.5%	24000
17-60-1	75%	100%	75%	100%	12000

Table (8.13) Summary of patients' differentiation success rate for Huntington's disease patients and their normal control subjects.

Number Of Units	Training Mode		Test Mode		Number Of Iterations
	Patients	Controls	Patients	Controls	
17-20-20-1	100%	100%	100%	100%	12000
17-25-25-1	100%	100%	100%	100%	12000
17-10-10-1	100%	100%	100%	100%	12000

8.4 Discussion

The success rate for the differentiation between HD patients and their normal control subjects was 100% in both the training and test modes. The alteration of the number of units in the hidden layers did not affect the success rates.

In the case of schizophrenic patients and their normal control subjects, one patient was falsely classified as normal. All the normal subjects were classified correctly. The alteration of number of units in the hidden layer(s) did not affect the success rates. In this branch of medicine the misclassification of a patient as normal is known as a "false-negative". In medical term the false-negative diagnosis is less serious than a "false-positive" diagnosis (ie. misclassification of a normal subject as patient) [Allen, 1989].

For PD patients and their normal control subjects, when the number of units in the hidden layer was 40, one normal subject was misclassified in the test mode but all the patients were classified correctly both in the training and test modes.

The alteration of number of units did not affect the success rates of identifying the patients because in each case a sufficient number of units were included in the neural networks.

8.5 Conclusion

The results indicated the particular time domain method of CNV feature extraction used in this chapter was effective in representing the CNV waveforms, and the application of neural networks was successful in identifying the schizophrenic, Parkinson's disease and Huntington's disease patients. The high success rates achieved were also due to the use of an evoked-potential (ie. the CNV) which was thought to be affected by the diseases under investigation.

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Chapter 9 Presymptomatic Detection of Huntington's Disease and Identification of Schizophrenic, PD and HD Patients by Applying Principal component Analysis and Cluster Analysis to the CNV

The methods described in chapters 7 and 8 to identify patients required a prior knowledge about the category of some of the patients. This enabled the methods to be trained on known patients and their normal control subjects. Then the classifiers used the information gained during the training together with the necessary CNV variables to identify test (unknown) patients. Some patients who are "at-risk" (AR) of HD may wish to know whether they will develop HD. This could help them to decide whether they should have children (a person diagnosed as HD gene carrier can pass on the faulty gene to his/her children). The methods described in chapters 7 and 8 could not be employed for presymptomatical detection of HD. This was because in order to form a classification (calibration) rule, they required the variables from the AR of HD patients who could be confirmed as the HD gene carriers (ie. the AR of HD patients who would develop HD). As this knowledge could not be obtained due to the difficulties associated with genetic testing and the unwillingness of many of the AR of HD patient to undergo it, it was decided to consider an alternative technique which did not require prior information about the patients (ie. an unsupervised learning).

The application of principal component analysis (PCA) and cluster analysis to the CNV waveforms of the schizophrenic, Parkinson's disease (PD) and Huntington's disease (HD) patients in order to evaluate their effectiveness in identifying the patients is described. These techniques were also applied to the CNV waveforms of the AR of HD patients with the aim of presymptomatically detecting HD. The CNV amplitudes of the AR of HD patients were also analysed using t-tests.

Cluster analysis is an unsupervised pattern recognition tool which could be used to discover possible associations and structure in the data. Diday and Simon [1976],

Everitt [1981] and Devijver [1982] have provided a review of clustering. Generally, the technique attempts to group the elements in such a way that there are high associations among the elements within a cluster, while different clusters are relatively distinct from each other ie. it aims at maximising the between-cluster variation relative to the within- cluster variation (see Figure (9.1)).

Before applying cluster analysis, a PCA of the discriminatory variables (ie. the CNV features) was carried out. This was necessary as otherwise a large number of clusters would have resulted making the interpretation of the results complicated. PCA transformed the variables in such a manner that the transformed variables (or the principal components) were linear combinations of the original variables. The successive linear combinations were uncorrelated with each other and accounted for successively smaller amounts of the total variation. PCA is described in more detail in section 9.1.

9.1 The Theory of Principal Component Analysis

The correlation matrix of the variables forms the starting point of a method for obtaining the principal components. If there are n individuals, and p variables (features) are obtained from the CNV response of each individual, the nxp data matrix can be represented by,

$$\mathbf{x} = \begin{bmatrix} x_{11} & x_{12} & \cdots & x_{1p} \\ x_{21} & x_{22} & \cdots & x_{2p} \\ \cdot & \cdot & \cdot & \cdot \\ \cdot & \cdot & \cdot & \cdot \\ \cdot & \cdot & \cdot & \cdot \\ x_{n1} & x_{n2} & \cdot & x_{np} \end{bmatrix}$$

where X_{ij} represents the value of variable j obtained from individual i. The method of calculating the correlation matrix (R) is described in Appendix (E).

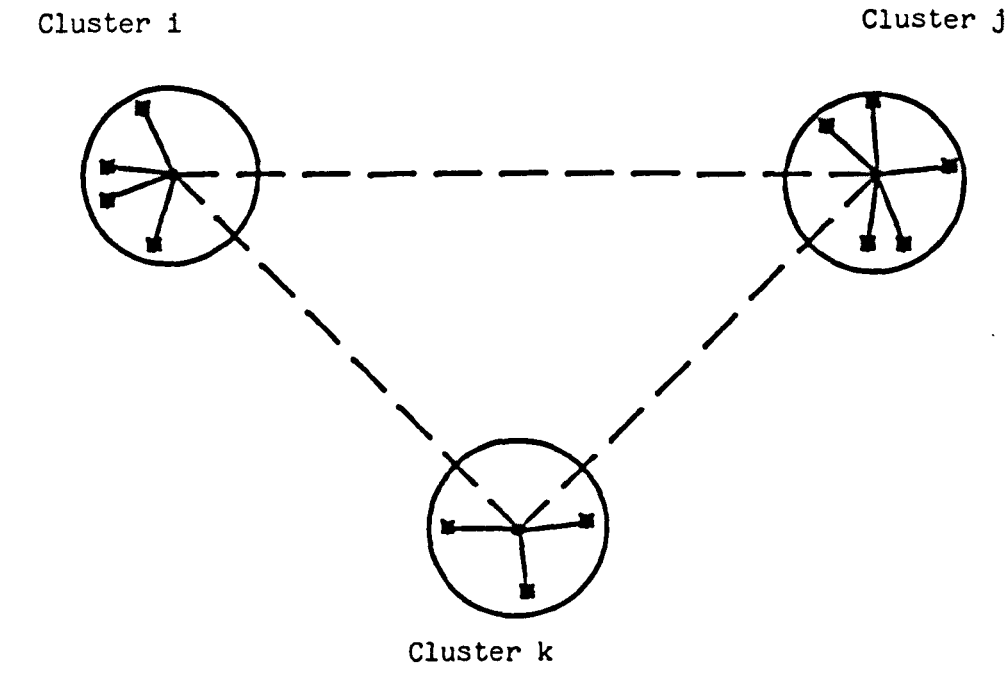

Figure 9.1 Representation of between - and within-cluster variation.

The procedure for computing the principal components using the correlation matrix is as follows.

i) The eigenvalues (ie. $\epsilon_1 \ldots \epsilon_p$) of the correlation matrix are obtained by solving,

$$|R - \epsilon I| = 0 \qquad \ldots(9.1)$$

where I is a matrix whose entries along the main diagonal are 1 and whose non-diagonal elements are 0 (ie. the unit matrix).

ii) The eigenvalues are then used in (9.2). For each eigenvalue (ϵ_i) a corresponding eigenvector (α_i) is obtained.

$$(R - \epsilon_i I)\alpha_i = 0 \qquad \ldots(9.2)$$

iii) The eigenvector corresponding to the largest eigenvalue (ie. α_1) is used to generate the first principal component (Y_1) for each individual. If α'_1 (note, the symbol' indicates transpose) is,

$$\alpha'_1 = (\alpha_{11}, \alpha_{12}, \ldots, \alpha_{1p})$$

then, Y_1 can be obtained by,

$$Y_1 = \alpha_{11}X_{11} + \alpha_{12}X_{12} + \ldots + \alpha_{1p}X_{1p} \qquad \ldots(9.3)$$

iv) The eigenvector corresponding to the next largest eigenvalue is used to generate the second principal component for each individual. This is repeated until all p principal components are generated.

The sum of the eigenvalues is equal to p (ie. the number of variables). The total variance of the variables provided by i^{th} principal component is indicated by ϵ_i/p, where ϵ_i is the i^{th} eigenvalue.

Mardia et al. [1979] and Morrison [1976] have provided a detailed analysis of PCA.

9.2 Theoretical Analysis of Clustering

Cluster analysis has been valuable in several applications in the medical field. Kendell [1968] applied clustering procedures to some depressive mental patients in order to examine the nature of depression. Jansen [1979] divided the EEG into segments and used a hierarchical clustering approach to group EEG segments of a number of types. A clustering algorithm has been incorporated in a computer system to aid clinicians in the interpretation of cranial magnetic-response images [Herskovits, 1990]. Farmer et al. [1983] used clustering methods to investigate whether schizophrenia is a heterogeneous condition. Morrison et al. [1990] used a hierarchical cluster analysis method in order to investigate positive and negative symptoms in schizophrenia.

There are numerous clustering methods. Gordon [1981] groups them into four types: partitioning methods, hierarchical methods, clumping methods and geometrical methods. Generally, a clustering method has some distinct characteristics which determine its applications. The main factors distinguishing the clustering methods are the parameters used to measure the distance between the elements and the algorithms applied to the distance measures to obtain the clusters [Cormack, 1971]. The hierarchical methods have been dominant in terms of their applications and the frequency of use [Blashfield and Aldenderfer, 1978]. A widely used hierarchical clustering method is Ward's method [Mojena, 1977]

[Bayne et al., 1980] and it was the method selected.

Ward [1963] proposed that the loss of information which resulted from clustering of elements could be measured by the within sum of square deviations of every point from the mean of the cluster it belonged. At each stage of the process, the fusion of every possible pair of existing clusters is considered and their respective within sum of square deviations (w) are calculated. The pair whose fusion results in the minimum increase in the w possible at that stage is selected and combined.

Consider a sample of n individuals to be partitioned into g groups. Then the value of w for the g-group partition is [Anderberg, 1973],

$$w = \sum_{i=1}^{i=g} \sum_{j=1}^{j=n_i} (x_{ij} - \bar{x}_i)^2 \qquad \ldots(9.4)$$

Where n_i is the number of elements in the i^{th} group, $\bar{x}_i$ is the mean of the variables in the i^{th} group and x_{ij} is the j^{th} variable in the i^{th} group.

Ward's method can efficiently be implemented by an algorithm described by Wishart [1969]. This algorithm is based on a stored matrix of squared Euclidean distances between the centroids of the clusters. Let d_{ij} be the squared Euclidean distance between the centroids of clusters i and j ie.

$$d_{ij} = \sum_{l=1}^{n} (x_{il} - x_{jl})^2 \qquad \ldots(9.5)$$

where x_{il} is the l^{th} variable on the i^{th} element, x_{jl} is the l^{th} variable on the j^{th} element and n is the number of elements. Then the distance between the fused clusters i and j, and a new cluster k has been shown to be [Anderberg, 1973] [Gordon, 1981],

$$d_{k(i,j)} = \frac{1}{n_k+n_i+n_j}\left[(n_k+n_i)d_{ki} + (n_k+n_j)d_{kj} - n_k d_{ij}\right] \quad \ldots(9.6)$$

where n_i, n_j, and n_k are the number of elements in the clusters i, j and k respectively, d_{ki}, d_{kj} and d_{ij} are the squared Euclidean distances between the clusters k and i, k and j, and i and j respectively.

The steps to implement the above recursive algorithm can be summarised as:

i) Obtain the squared Euclidean distance matrix for each pair of elements in the data set using the formula (9.5).
ii) Amalgamate (fuse) the two elements with smallest value of squared Euclidean distance.
iii) Recalculate the distances between the new cluster and every other cluster (initially other clusters contain only one element) using the formula (9.6). Fuse the two clusters with smallest value of $d_{k(i,j)}$ or d_{ij}.
iv) Repeat step (iii) until all elements are finally within one cluster.

9.3 Experimental Procedure

Seventeen variables (features) were extracted from the preprocessed averaged (over 8 CNV trials) CNV waveform from each individual. The method was described in chapter 8. The details related to the age, sex, medication and the number of patients and their normal control subjects were given in chapter 8, Tables (8.1)-(8.3).

PCA was implemented using the SAS [1985] procedure, Princomp. For each patient category a program was written in the format described in SAS [1985]. In the programs the procedure Princomp was invoked. The method generated

seventeen principal components (the number of principal components were equal to the number of original variables), sorted by descending order of eigenvalues which were equal to total variance for the variables representing each subject category. Generally, the first few principal components account for most of the total variance of the variables. In order to determine how many components should be retained the eigenvalues of the principal components may be considered [SAS, 1985]. Table (9.1) shows the eigenvalues of the seventeen principal components for each subject category.

Table (9.1) The eigenvalues for schizophrenic (sch.), Parkinson's disease (PD), Huntington's disease (HD) and at-risk (AR) of HD patients and their normal control subjects.

Principal Component Number	Eigenvalue			
	Sch.	PD	HD	AR OF HD
1	13.9620	13.7598	14.1895	13.5663
2	1.1098	1.3174	1.0647	1.2998
3	0.8683	0.7656	0.9269	0.7361
4	0.2773	0.4635	0.5650	0.4653
5	0.2462	0.2633	0.1122	0.3774
6	0.2132	0.1701	0.0932	0.2154
7	0.1388	0.1145	0.0283	0.2014
8	0.0666	0.0945	0.0121	0.0687
9	0.0567	0.0305	0.0040	0.0376
10	0.0499	0.0100	0.0022	0.0192
11	0.0091	0.0073	0.0017	0.0099
12	0.0017	0.0030	0.0001	0.0021
13	0.0005	0.0003	0.0000	0.0006
14	0.0000	0.0001	0.0000	0.0001
15	0.0000	0.0000	0.0000	0.0000
16	0.0000	0.0000	0.0000	0.0000
17	0.0000	0.0000	0.0000	0.0000

As can be seen from the Table (9.1), the first principal component accounted for 82.13% (ie. 13.9620 x 17/100), 80.94% (ie. 13.7598 x 17/100), 83.47% (ie. 14.1895 x 17/100) and 79.80% (ie. 13.5663 x 17/100) of total variance for schizophrenic, PD, HD and AR of HD patients respectively. Tables (9.2)-(9.5) provide a list of the first three principal components for the patients and their normal control subjects.

Table (9.2) The first three principal components for the schizophrenic patients and their normal control subjects.

No.	Schizophrenic Patients			Normal Control Subjects		
	Prin1	Prin2	Prin3	Prin1	Prin2	Prin3
1	3.1439	0.6188	-0.0166	-6.4906	0.8735	-0.5572
2	0.7557	1.4672	2.0356	-1.4385	-1.3162	0.1802
3	4.9198	-0.6122	-0.4076	0.2079	1.2097	-1.1990
4	4.0882	2.0208	2.5334	-1.4772	0.7222	-1.3836
5	4.6672	-1.6697	0.5902	-2.3331	0.6742	-0.3407
6	1.2497	-0.7707	1.2813	-1.3937	0.3666	-1.1251
7	-0.7849	-1.4605	0.4416	-1.0188	-0.1795	-0.4162
8	6.1618	-1.7724	-0.1197	-5.9887	-0.3671	0.6989
9	3.6784	-0.7551	0.1059	-2.4373	-0.8361	0.3666
10	3.0878	-0.8129	0.2222	-9.4948	-0.2699	1.8302
11	4.8197	0.5211	0.0771	-2.2191	-1.0371	0.1824
12	1.4378	-1.5897	0.6431	1.2139	0.4149	-0.4228
13	2.9294	-0.6146	-0.5826	-4.5109	0.3544	-0.7263
14	2.5190	-0.8141	-0.6021	-3.9725	-0.4772	-0.3424
15	5.6023	-0.1583	-1.0533	-1.4803	0.1963	-0.9400
16	2.7751	1.6170	1.9050	-0.4616	0.6249	-1.5605
17	-2.5536	-1.8421	0.2197	-3.5131	0.4028	0.0318
18	1.7452	2.1328	-0.3339	-2.8858	0.8438	-0.8836
19	2.7525	1.5865	-0.1293	-6.2068	-0.1333	0.5708
20	4.3294	0.7192	-0.2525	-1.4234	0.1220	-0.5212

Table (9.3) The first three principal components for Parkinson's disease patients and their normal control subjects.

No.	Parkinson's Disease Patients			Normal Control Subjects		
	Prin1	Prin2	Prin3	Prin1	Prin2	Prin3
1	-2.7164	2.5151	0.2937	1.3655	-0.2754	-0.8598
2	0.8067	-0.7438	-0.3671	-3.1420	-1.7281	0.7468
3	-0.0722	-0.4517	0.4310	-6.0761	-0.0114	-0.6934
4	2.1997	-1.5230	-0.1309	-2.1241	-2.2266	0.8024
5	3.0660	1.2585	1.2932	-8.3803	-0.6864	1.1519
6	4.4560	-1.6549	1.0678	-2.0374	0.9020	-1.6084
7	3.4589	1.1835	0.0726	-2.0067	-0.0918	-1.0734
8	6.0574	0.0489	0.3626	-0.3864	-1.1807	0.0948
9	7.3420	0.3296	0.2573	1.3715	0.1183	-0.0292
10	-3.2442	1.8487	1.7611	-2.0955	-0.1580	-0.8437
11	5.0973	0.9983	0.3616	-3.9974	1.1033	-0.1555
12	-3.7084	1.6599	0.8432	-1.1847	0.6524	-1.3280
13	1.3913	-0.5667	-0.2010	3.3615	0.5128	-1.7409
14	1.4412	1.2461	0.6644	-5.4337	-1.1489	-0.0911
15	5.4170	-0.8926	-0.0752	-0.7781	0.1823	-1.5936
16	1.0778	0.1017	0.5330	-0.5262	-1.3214	0.0537

Table (9.4) The first three principal components for the Huntington's disease patients and their normal control subjects.

No.	Huntington's Disease Patients			Normal Control Subjects		
	Prin1	Prin2	Prin3	Prin1	Prin2	Prin3
1	1.8409	3.2200	1.0080	-2.6636	-0.0471	0.2307
2	-0.1936	0.7218	-3.5513	-1.8322	-0.3416	-0.0947
3	0.8721	0.3163	0.1501	-5.9894	0.4334	0.0688
4	5.6909	0.5613	-1.4752	-2.1769	-0.0879	-0.2552
5	3.9022	-0.0143	-0.3494	-2.4530	-0.9007	0.5138
6	-1.1992	1.4641	0.6457	-3.1980	0.0693	0.1848
7	-0.7307	1.1075	0.7348	0.5472	-1.5773	0.2049
8	1.6552	-0.0176	0.2118	-2.6332	-0.8075	0.3585
9	11.3673	-0.6912	1.2257	-3.4531	-0.4984	-0.0259
10	4.1069	-1.1885	-0.4527	-1.6673	-0.3585	0.3977
11	0.6091	-0.3524	0.0571	-2.4017	-1.0107	0.2119

Table (9.5) The first three principal components for the at-risk of Huntington's disease patients and their normal control subjects.

No.	AR OF HD Patients			Normal Control Subjects		
	Prin1	Prin2	Prin3	Prin1	Prin2	Prin3
1	-2.1980	-0.8940	-1.1799	-1.2639	0.4959	0.5352
2	-7.1123	-1.0787	0.6781	-8.3460	1.8752	-0.1492
3	-0.7756	0.6503	2.1144	-5.2044	-0.5877	-0.4017
4	6.4037	0.0179	-0.0847	-1.8097	-0.4033	-0.2940
5	5.1512	-0.2440	-0.9720	2.3617	-1.7546	0.6369
6	0.5698	-1.2822	-0.3554	-3.5237	-0.0830	-0.7131
7	3.0356	-0.3529	-0.9810	1.1724	-1.0623	0.0683
8	0.9374	0.3776	1.2092	0.2625	0.4508	-0.9820
9	4.4420	1.1833	0.5425	-2.4105	-1.1313	0.6714
10	1.0391	1.3914	-0.7114	-0.6818	-0.6648	-0.3197
11	6.4191	0.3081	0.0889	-4.4313	0.5522	-0.1051
12	4.2718	1.8809	0.0625	1.1811	-0.2544	0.2640
13	1.3321	-1.3167	0.5414	-0.5195	-1.3738	-0.0871
14	-1.0447	0.2922	0.4182	2.4911	-0.0127	-0.9429
15	-3.4573	0.4005	-0.5521	3.1268	-0.9514	1.8443
16	3.4998	2.1746	0.4779	-4.4050	2.6182	1.5008
17	3.0911	2.3037	0.5568	-4.7351	-1.1590	0.2320
18	-2.3812	1.8358	-2.2575	1.7342	-0.3975	-0.5955
19	4.4145	-0.9284	-0.7160	-4.1468	0.5132	-0.9314
20	5.4499	-0.3876	-0.6534	1.2640	-1.2993	0.4317
21	-4.6896	-1.1961	0.0595	-0.5146	-0.5061	1.0508

It was decided first to investigate the use of the first principal component in the cluster analysis as it accounted for about 80% of the total variance for all four subject categories (ie. schizophrenia, PD, HD and AR of HD). Each of the remaining principal components accounted for less than 8% of the total variance. The effects of the second and third principal components were also examined. They did not improve the analysis result. Therefore the first principal component was the only component retained.

A clustering computer package program called Clustan [Wishart, 1987] [Using Clustan under VM/CMS, 1987] was available. Ward's clustering method was implemented by using a Clustan procedure called Cluster. For each patient category a program was written in accordance with the Clustan instructions. The

listings of these programs are shown in Appendix (F). In each program the procedure Cluster was invoked. The execution of each program produced a tree-diagram called the "dendrogram". The subjects' identifiers were printed at the end of the branches and the fusion coefficients as indicated by the formulae (9.5) and (9.6) were shown on the sides of the dendrograms.

9.4 Results and Discussion

9.4.1 Schizophrenia

The dendrogram for the schizophrenic patients and their normal control subjects is shown in Figure (9.2). The schizophrenic patients were labelled 1 to 20 and their normal control as 21 to 40. Two main clusters, C_1 and C_2 were identified corresponding to the fusion coefficient of 0.440. The cluster C_1 contained 18 schizophrenic patients and 2 normal subjects. The cluster C_2 contained 18 normal subjects and 2 schizophrenic patients.

9.4.2 Parkinson's Disease

The dendrogram for the PD patients (labelled as 1-16) and their normal control subjects (labelled 17-32) is shown in Figure (9.3). Two main clusters, C_1 and C_2 were identified corresponding the fusion coefficient of 0.326. C_1 contained 13 normal subjects and 4 PD patients and C_2 contained 12 PD patients and 3 normal subjects.

9.4.3 Huntington's Disease

The dendrogram for the HD patients (labelled as 1 to 11) and their normal control subjects as (12 to 22) is shown in Figure (9.4). Three clusters C_1, C_2 and C_3 were identified corresponding to the fusion coefficient of 0.131. The clusters C_1 and C_3 contained all the HD patients. The normal subjects, with the exception of subject 18 were included in cluster C_2.

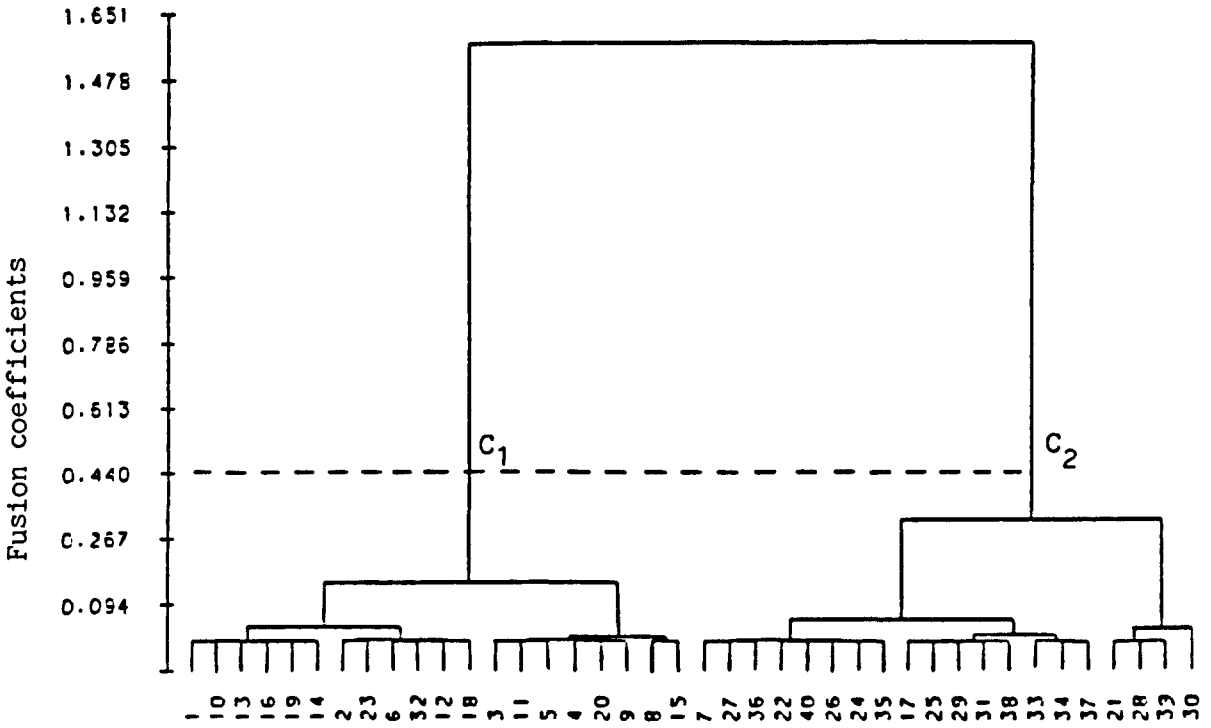

Figure 9.2 The dendrogram for identification of the Schizophrenic patients.

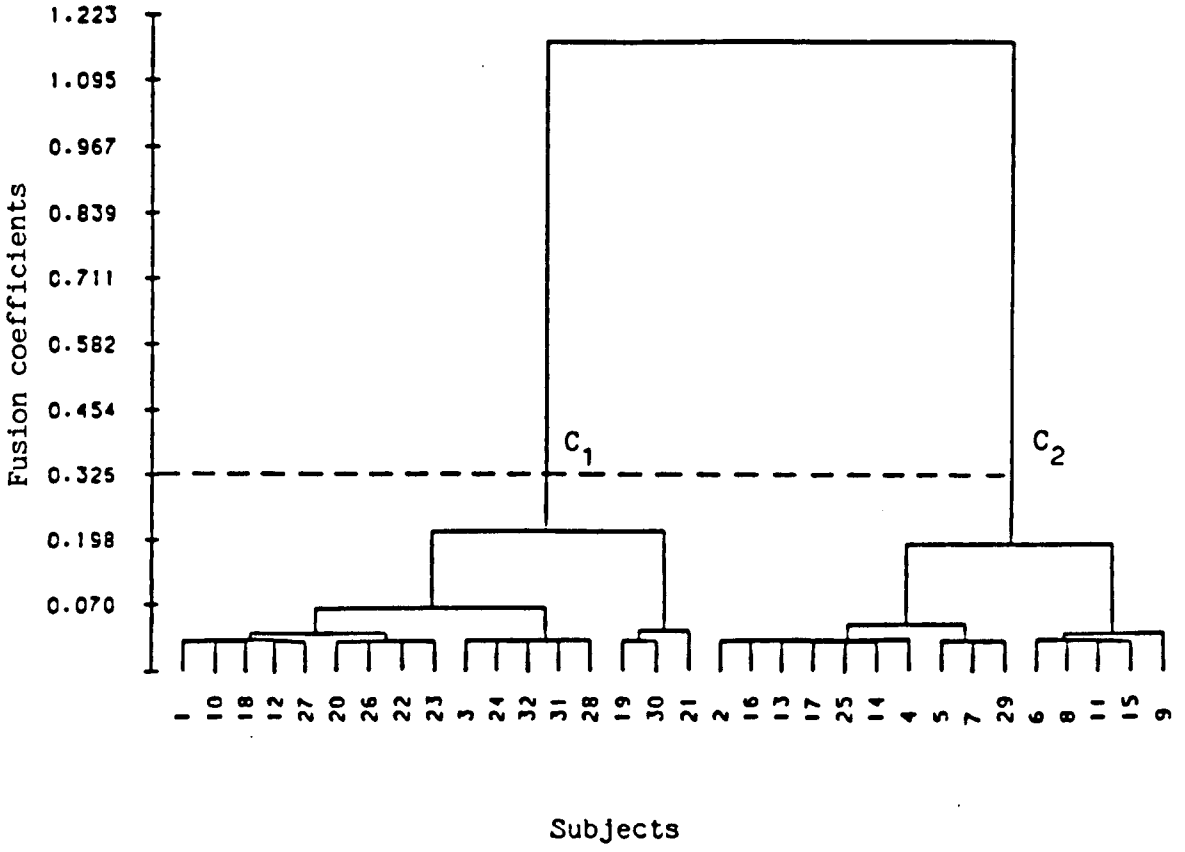

Figure 9.3 The dendrogram for identification of the Parkinson's disease patients.

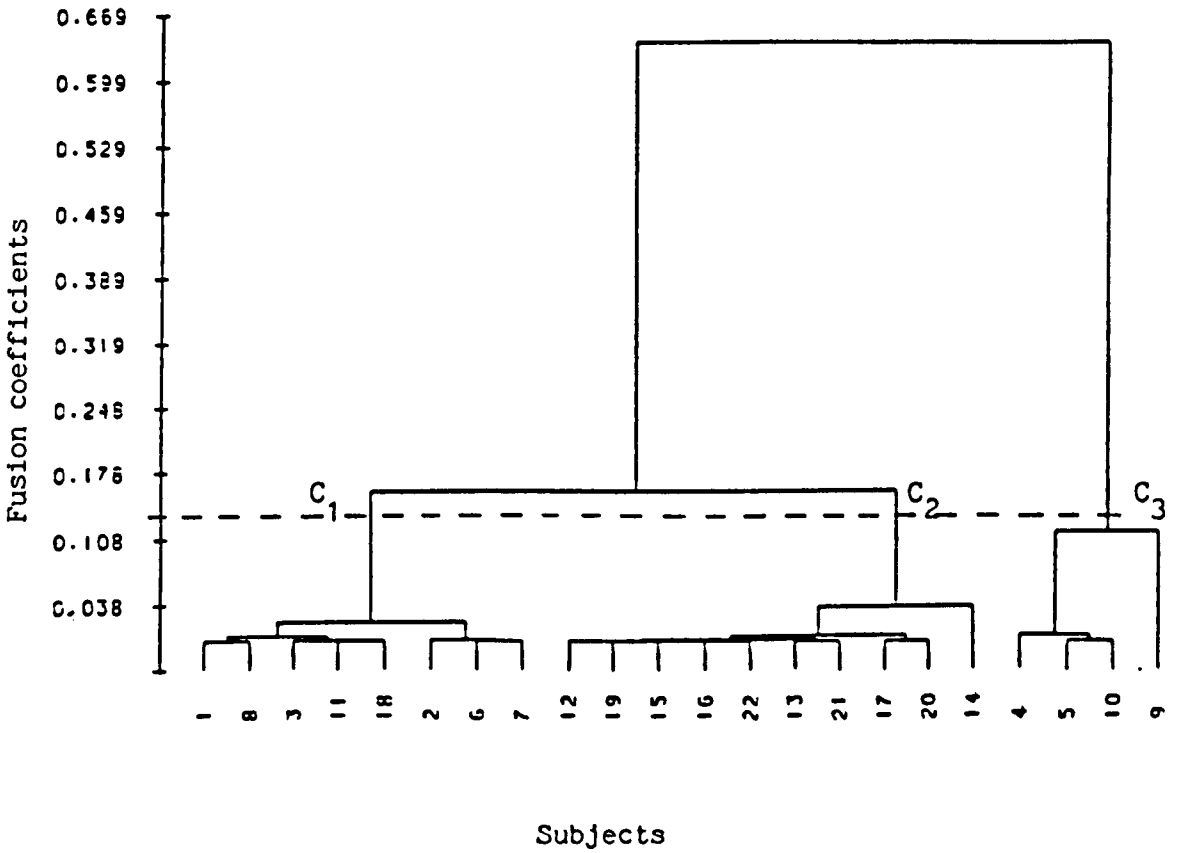

Figure 9.4 The dendrogram for identification the of Huntington's disease patients.

9.4.4 At-risk of Huntington's Disease

The dendrogram for the AR of HD patients is shown in Figure (9.5). The AR of HD patients were labelled as 1 to 21 and their normal control subjects were labelled as 22 to 42. Four clusters C_1, C_2, C_3 and C_4 were identified corresponding to the fusion coefficient of 0.145. Seven AR of HD patients were in C_3. The other clusters contained a mixture of AR of HD patients and normal subjects. Therefore it was concluded that the 7 AR of HD patients in cluster C_3 had CNV responses which were significantly different from the CNV responses of normal subjects and the remaining AR of HD patients. The AR of HD patients in cluster C_3 were labelled as abnormal AR of HD patients, the remaining AR of HD patients were labelled as normal AR of HD patients.

9.5 CNV Amplitude Analysis of the At-Risk of Huntington's Disease Patients

The CNV amplitudes of the AR of HD patients and their normal control subjects were analysed using a two tailed t-test in order to determine whether the results would agree with the principal component analysis and cluster analysis findings. In order to reduce the effect of the background EEG, the CNV amplitude is generally expressed as a mean value of the samples from a section prior to the imperative-stimulus [McCallum and Walter, 1968]. Therefore, the CNV amplitudes were obtained from preprocessed averaged (over 8 trials) CNV waveforms by averaging 16 samples values prior to the imperative stimulus. The listing of the program used to obtain the CNV amplitude is given in Appendix (G).

As the data used in a t-test analysis should have a normal distribution [Kennedy and Neville, 1986], the variables were initially examined for statistical distribution using the SAS [1985] Univariate procedure. If they did not have a normal distribution, they were transformed using the function $f(x) = -1/x$. This function is effective when there are a number of variables with values much larger than the group's mean [Bland, 1987].

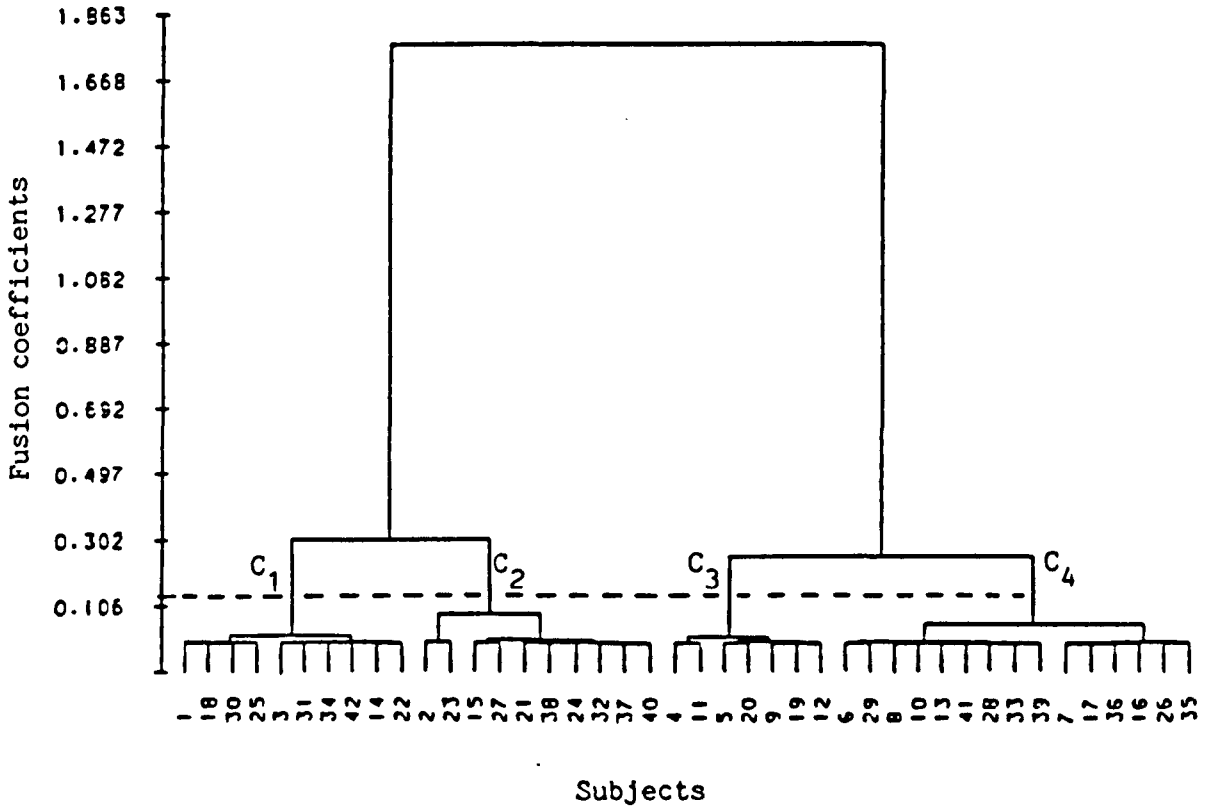

Figure 9.5 The dendrogram for identification of the at-risk of Huntington's disease patients.

The CNV amplitudes of the AR of HD patients were compared with the CNV amplitudes of their normal control subjects (refer to Table (9.6)).

Table (9.6) The CNV amplitude analysis of the AR of HD patients and their normal control subjects.

Category	Number	Mean Age (STD)	Number On Drug	Mean CNV Amplitude	T-Test Result
at-risk of HD patients	21	36.43 (17.12)	2	-13.21μV	$p<0.01$ df=40
normal control subjects	21	37.57 (10.22)	0	-18.53μV	

It was found their amplitudes were significantly different from the CNV amplitudes of the normal subjects ($p<0.01$, $df=40$).

The mean CNV amplitudes of the normal and abnormal of AR of HD patient group and those of their normal control subjects are shown in Table (9.7) and their t-test analysis results are shown in Table (9.8).

Table (9.7) The mean CNV amplitudes of the normal and abnormal AR of HD patient groups and those of their normal control groups.

Category		Number	Mean Age (STD)	Number On Drug	Mean CNV Amplitude (STD)
AR of HD patients	abnormal	7	41.6 (13.0)	1	-6.23μV (1.15)
	normal	14	33.9 (18.8)	1	-16.70μV (5.57)
normal control subjects	for the abnormal AR of HD patients	7	40.3 (10.0)	0	-18.16μV (3.73)
	for the normal AR of HD patients	14	36.2 (10.5)	0	-18.71μV (5.07)

Table (9.8) The CNV amplitude analysis results of the normal and abnormal AR of HD patients.

Category	T-Test Result	Degrees Of Freedom
abnormal AR of HD versus normal controls	$p<0.001$	12
normal AR of HD versus normal controls	$p=0.328$	26
abnormal AR of HD versus normal AR of HD	$p<0.001$	19

The mean CNV amplitude of the abnormal AR of HD patient group was less than the mean CNV amplitude of their normal control group. It was also less than the mean CNV amplitude of the normal AR of HD patient group. T-test analysis indicated that the differences between the CNV amplitudes of the abnormal AR of HD patients and their normal control subjects were significant at 1% level, df=12 (refer to Table (9.8)). The differences between the CNV amplitudes of the

abnormal and normal AR of HD patients were also significant ($p<0.001$, $df=19$). The difference between the mean CNV amplitude of the normal AR of HD patient group and their normal control group was not significant. Therefore, the results of the CNV amplitude analysis were in agreement with the principal component analysis and cluster analysis findings.

As the HD patients have abnormal CNV waveforms [Jervis et al., 1984] [Jervis et el., 1989] and considering the above results it might be possible to suggest that the 7 abnormal AR of HD patients would develop HD.

9.6 Conclusion

It was possible to identify the majority of schizophrenic, PD and HD patients by applying principal component analysis and cluster analysis to the CNV waveforms. The application of the method to 21 AR of HD patients resulted in the identification of 7 abnormal AR of HD patients. The CNV analysis indicated that the CNV amplitude in the 7 abnormal AR of HD patients was significantly different from that in normal control subjects.

The effectiveness of this method in presymptomatically detecting HD patients will have to be further evaluated to establish the sensitivity and the reliability of the method.

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Chapter 10 Reaction Times Analysis of Schizophrenic, Parkinson's Disease, Huntington's Disease and At-Risk of Huntington's Disease Patients

Reaction time represents the ability of a subject to respond to a stimulus. This process may be affected by brain structural abnormalities caused by disorders such as schizophrenia, PD and HD. For example, Yokochi et al. [1985] reported the prolongation of reaction times in PD patients. The prolongation of reaction times in PD patients has been attributed to the changes in the functional loops of the basal ganglia related to motor behaviour [DeLong et al., 1983].

Reaction time may also represent the efficiency of a subject in processing information. Baribeau-Braun et al. [1983] analysed the reaction times of schizophrenic patients in an experiment involving the detection of an occasional target tone among frequent standard tones. They reported that the reaction times of the schizophrenic patients were longer than the reaction times of their normal control subjects. In the same study it was suggested that the prolongation of reaction times of schizophrenic patients might be due to the inefficiency of the schizophrenic patients in organising and processing information.

Some studies have indicated that there may be a relationship between CNV magnitude and reaction time value. A review some of these findings was provided by Tecce [1972]. The general view has been that reaction time tends to be shorter following a CNV with large amplitude and longer following a low amplitude CNV.

During the data recording, the reaction times of each subject to 32 stimuli were measured. In this chapter the reaction times of schizophrenic, PD, HD and AR of HD patients are compared with the reaction times of their normal control subjects. The aim was to investigate whether schizophrenia, HD and PD alter the reaction time of the patient to the stimulus. This analysis is then extended to consider how

the findings relate to the two groups of AR of HD patients identified in chapter 9.

10.1 The Method of Analysis and Results

The mean of 32 reaction times (in seconds) for the patients and their normal control subjects are shown in Tables (10.1a)-(10.1d).

Table (10.1a) The averaged reaction times of the schizophrenic (Sch.) patients and their normal control subjects.

Subject Number	Sch. Patients	Normal Controls
1	0.449	0.187
2	0.388	0.309
3	1.845	0.168
4	0.633	0.206
5	0.654	0.260
6	0.285	0.176
7	0.321	0.273
8	0.653	0.177
9	0.261	0.264
10	0.393	0.179
11	0.268	0.302
12	0.477	0.272
13	0.324	0.201
14	0.299	0.139
15	0.329	0.197
16	0.192	0.156
17	0.203	0.150
18	0.630	0.326
19	0.312	0.175
20	0.171	0.177

Table (10.1b) The averaged reaction times of the Parkinson's disease (PD) patients and their normal control subjects.

Subject Number	PD Patients	Normal Controls
1	0.288	0.275
2	0.397	0.302
3	0.366	0.201
4	0.566	0.309
5	0.261	0.175
6	0.300	0.206
7	0.325	0.176
8	0.319	0.214
9	0.589	0.272
10	0.309	0.197
11	0.347	0.386
12	0.247	0.212
13	0.350	0.320
14	0.271	0.139
15	0.381	0.156
16	0.340	0.196

Table (10.1c) The averaged reaction times of the "at-risk" of Huntington's disease (AR of HD) patients and their normal control subjects.

Subject Number	AR OF HD Patients	Normal Controls
1	0.365	0.150
2	0.256	0.179
3	0.313	0.221
4	0.308	0.139
5	0.261	0.156
6	0.279	0.566
7	0.267	0.197
8	0.265	0.272
9	0.288	0.275
10	0.581	0.207
11	0.244	0.175
12	0.207	0.177
13	0.184	0.326
14	0.204	0.393
15	0.242	0.168
16	0.246	0.346
17	0.305	0.187
18	0.141	0.273
19	0.151	0.177
20	0.244	0.176
21	0.320	0.386

Table (10.1d) The averaged reaction times of the Huntington's disease (HD) patients and their normal control subjects.

Subject Number	HD Patients	Normal Controls
1	0.501	0.309
2	0.915	0.393
3	0.731	0.175
4	0.651	0.181
5	4.935	0.176
6	0.826	0.302
7	1.192	0.320
8	0.529	0.175
9	2.495	0.386
10	0.278	0.214
11	0.369	0.206

Table (10.2) shows the mean reaction time and its standard deviation (STD) for each subject category.

Table (10.2) The mean reaction time values and the standard deviations (STDs) of the patients and their normal control subjects.

Category	Mean Age (STD)	Number of Subjects	Reaction Times (sec.)	
			Mean	STD
schizophrenic patients	33.60 (12.22)	20 (15 male)	0.454	0.362
normal control subjects	39.50 (13.66)	20 (15 male)	0.215	0.058
Parkinson's disease patients	63.63 (9.68)	16 (10 male)	0.354	0.097
normal control subjects	50.81 (11.16)	16 (10 male)	0.234	0.069
at-risk of Huntington's disease Patients	36.43 (17.12)	21 (10 male)	0.270	0.090
normal control subjects	37.57 (10.22)	21 (10 male)	0.245	0.107
Huntington's disease patients	53.73 (10.97)	11 (6 male)	1.220	1.373
normal control subjects	50.09 (10.53)	11 (6 male)	0.258	0.086

Tests were carried out using the SAS [1985] Univariate procedure to examine the statistical distribution of the reaction times. The Univariate procedure plotted the distribution of each data set together with a cure indicating where normally distributed data should fall. It also provided a parameter W which indicated whether or not the data had a normal distribution. The value of W was between 0 and 1. Small values of W indicated that the data were not normally distributed. The test for distribution of the data was necessary as the t-test was applicable when the reaction times had a normal or nearly normal distribution, though the two-tailed t-test used is less affected by this condition compared with the one-

tailed t-test [Kennedy and Neville, 1986]. The Univariate procedure indicated the statistical distributions in all subject categories were not normal and therefore they required transformation to the normal distribution. Two transformation functions, $f(x)=-1/x$ and $f(x)=\log_e(x)$ were suitable for this purpose [Bland, 1987]. They were selected as in each case a few reaction times were comparatively much larger than the rest, and these transformation functions reduce the large values more than those of central or small values. The distributions of each data set after transformation by $-1/x$ and $\log_e(x)$ were examined. The transformation which provided a closer fit to the normal distribution was then selected. After transformation the distributions in all cases were close to the normal distribution. Table (10.3) indicates the transformation function used for each patient category.

Table (10.3) The t-test results for the reaction times of the patient categories.

Category	Transformation Function f(x)	T-Test Results
schizophrenic patients versus normal control subjects	$-1/x$	$p<0.001$ (df=38)
Parkinson's disease patients versus normal control subjects	$\log_e(x)$	$p<0.001$ (df=30)
at-risk of Huntington's disease patients versus normal control subjects	$-1/x$	$p=0.1480$ (df=40)
Huntington's disease patients versus normal control subjects	$-1/x$	$p<0.001$ (df=20)

A two-tailed t-test was then applied to the (transformed) reaction times. This test was used as the aim was to establish whether the mean reaction time of each patient category differed significantly from the mean reaction time of the normal

control category. The t-test was carried out using the SAS [1985] Ttest procedure. The results are shown in Table (10.3).

In chapter 9 the AR of HD patients were divided into abnormal (n=7) and normal (n=14) groups and it was suggested that the 7 abnormal AR of HD patients would develop HD. The mean reaction times of the two groups of AR of HD patients and their normal control subjects are shown in Table (10.4).

Table (10.4) The mean reaction time values in the normal and abnormal at risk of Huntington's disease (AR of HD) patients and their normal control subjects (std = standard deviation).

Category	Mean Age (STD)	Number of Subjects	Reaction Times (sec.)	
			Mean	STD
normal AR of HD patients	33.86 (18.74)	14 (4 male)	0.284	0.103
normal control subjects	36.21 (10.45)	14 (4 male)	0.277	0.116
abnormal AR of HD patients	41.57 (13.02)	7 (6 male)	0.243	0.052
normal control subjects	40.29 (9.96)	7 (6 male)	0.182	0.043

The reaction times did not have a normal distribution and therefore they were transformed using the function $f(x)=-1/x$. The t-test results are shown in Table (10.5).

Table (10.5) The t-test results for the reaction times of the abnormal and normal AR of HD patients.

Category	Transformation Function f(x)	T-Test Result
abnormal AR of HD patients versus normal control subjects	-1/x	p<0.05 (df=12)
normal AR of HD patients versus normal control subjects	-1/x	p=0.6263 (df=26)

10.2 Discussion

The mean reaction times in descending order of magnitude were: 1.220s (for HD patients), 0.454s (for schizophrenic patients), 0.354s (for PD patients) and 0.270s (for AR of HD patients).

The mean reaction times of the schizophrenic, PD and HD patient groups were significantly different from the mean reaction times of their normal control groups ($p<0.001$).

The mean reaction times of the AR of HD patients were not significantly different from the mean reaction times of their normal control subjects. But the mean reaction times of the 7 abnormal AR of HD patients were significantly different from the mean reaction times of their normal control subjects ($p<0.05$, $df=12$). The mean reaction times in the 14 normal AR of HD patients on the other hand were not significantly different from their normal control subjects.

Although the reaction times of the schizophrenic, PD and HD patients were significantly different from the reaction times of normal control groups, the value

of the reaction time on its own might not provide an accurate measure for identifying the patients. This is because factors not related to the diseases may affect its value, eg. if a person has been involved for a long period in a task which required responding to a stimulus then the reaction time of that person would generally be less than others.

10.3 Conclusion

The results in this chapter indicated that the reaction time may well be affected by schizophrenia, PD and HD. The reaction time analysis of the normal and abnormal AR of HD patients indicated the reaction time was affected in the abnormal AR of HD patients. This result was in agreement with the finding of chapter 9 which indicated that the CNV amplitude was also affected in that category.

Whether it would be desirable to include the reaction time as one of the discriminatory features (described in chapters 7, 8 and 9) for identifying the patients requires further investigation.

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Chapter 11 Comparison of the Methods Used to Identify Schizophrenic, Parkinson's Disease and Huntington's Disease patients

The method which involved application of discrete Fourier transform and discriminant analysis was as effective as the neural network method in distinguishing the patients from normal control subjects. It also made it possible to differentiate between the individuals from one patient category from another.

The neural network method reduced the complexity of distinguishing between the patients from the three categories and their normal control subjects. It also reduced the processing time. The leave-one-out method of analysing data used in the discriminant analysis method was not implemented when using neural networks because neural networks required a much longer time for their training phase.

The method involving the application of principal component analysis and clustering was not as effective as the other two methods in identifying the schizophrenic, PD and HD patients. But, it made it possible to identify 7 abnormal AR of HD patients from 21 AR of HD patients. This method required the least processing time compared to the two other methods of patient identification.

Taking into account the implementation complexity and success rates of each method in identifying the patients, it is preferable to use the neural network method for the identification of schizophrenic, PD and HD patients.

Chapter 12 Further Studies

As this study was based on a limited number of patients and normal subjects, it will be necessary to test the methods on a larger number of individuals in order to establish whether they can be used as routine clinical tests for differentiating between schizophrenic, PD, HD patients and normal subjects.

Some of the patients included in this study were on medication related to their disorders. Therefore an analysis of the effects of medication on the patient identification results should be carried out to determine if the medication had any effect on the test results.

It would be useful to include patients with other disorders, such as manic depression, and investigate whether the methods discussed could be used for their detection. The CNV responses of two patients with manic depression were recorded during the course of this study and a prolonged PINV was observed in one of them (see Figure (12.1)).

A follow up of the AR of HD patients is required to establish the effectiveness of the principal component analysis and clustering in presymptomatically identifying HD patients. As some neural networks such as Kohonen networks [Aleksander and Morton, 1990], can operate in an unsupervised learning mode, an investigation could be carried out, based on the CNV, to determine the effectiveness of those neural networks in presymptomatically detecting HD.

The application of neural networks could be extended to distinguish between the schizophrenic, PD and HD patients.

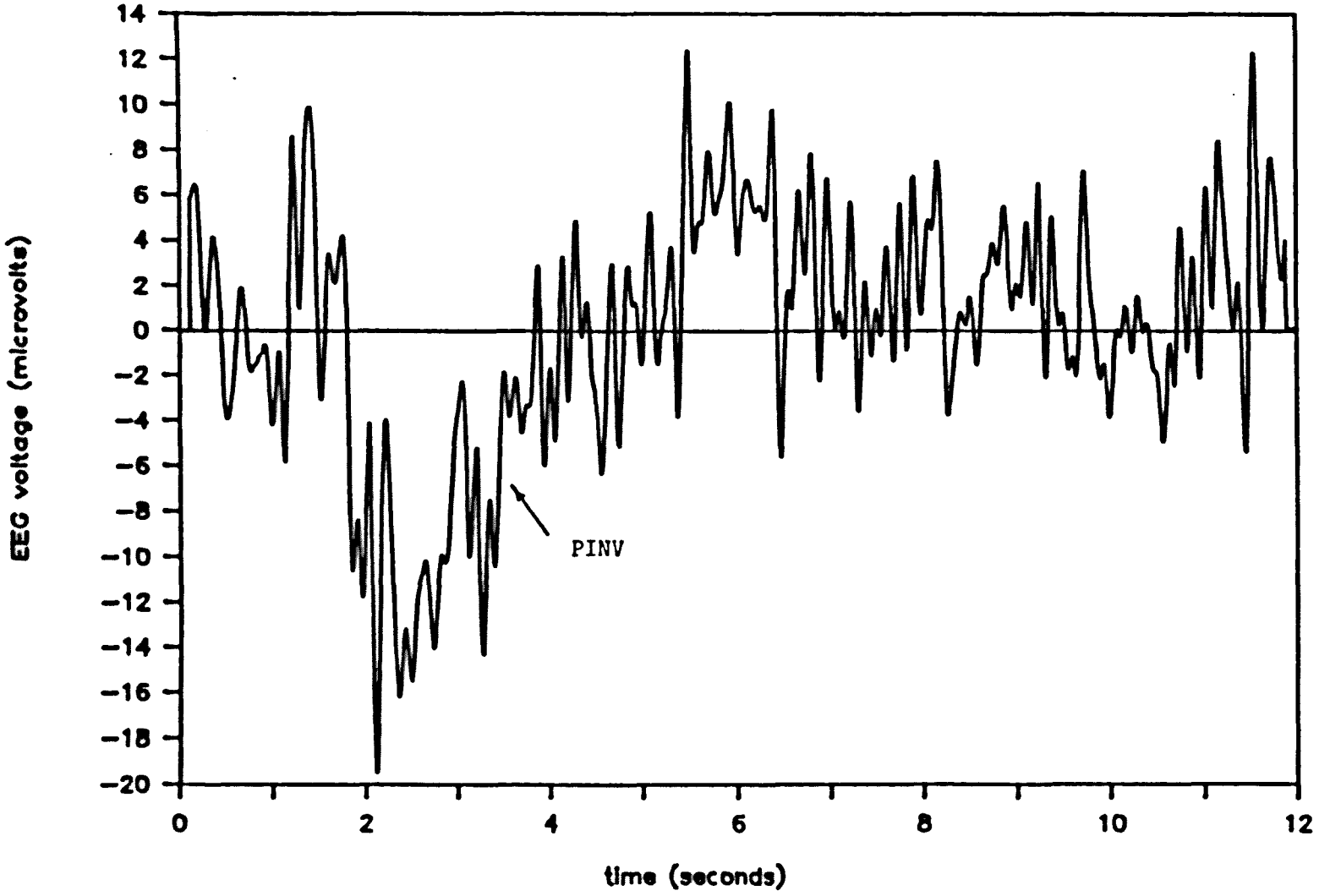

Figure 12.1 The preprocessed averaged CNV response in a manic depressive patient.

Reference

Aleksander, I and Morton, H., (1990), "An introduction to neural computing", Chapman and Hall, 148-155.

Chapter 13 Conclusion

An 8-channel instrumentation system suitable for the recording of the contingent negative variation (CNV), electrooculogram (EOG), electrocardiogram (ECG) and psychogalvanic response (PGR) was designed, constructed and tests showed that it met the required specifications. The system was successfully used to record the above named signals from 20 schizophrenic patients, 16 Parkinson's disease (PD) patients, 11 Huntington's disease (HD) patients, 21 at-risk of HD patients, and 43 normal control subjects. A feature of this instrumentation system was that it had a gain scheduling circuit. This caused the magnitude of the signal recorded from each channel to be checked for each sample and thus an appropriate gain which reflected the magnitude of the signal for that particular sample to be utilised. The gain scheduling was important as the signal of interest (ie. the CNV which has on average a magnitude of about -20μV) is susceptible to contaminations by much larger ocular artefact potentials. The ocular artefact potentials can have a magnitude of several hundred microvolts. Therefore, the gain scheduling process improved the accuracy of digitising the CNV signal.

Three different methods were successfully employed to differentiate between schizophrenic, PD, HD patients and normal subjects. The first method involved frequency analysis and discriminant analysis of the CNV waveform. It provided the following success rates:

- All HD patients were successfully distinguished from normal subjects (ie. 100% success rate).
- When differentiating between schizophrenic patients and normal subjects, all but one schizophrenic patients (ie. 95%) and all normal subjects (100%) were successfully identified.
- When differentiating between PD patients and normal subjects, 15 out of the

16 PD patients (93.8%) and 14 out of the 16 matched normal control subjects (87.5%) were successfully identified.

The method of frequency analysis and discriminant analysis of the CNV waveform was also effective in differentiating between schizophrenic, HD and PD patients. The success rates obtained when differentiating between the patients from these three patient categories were always higher than 81% and on average less than the success rates achieved when differentiating between the patients and normal subjects. This may suggest that some of the CNV abnormalities produced as a result of these disorders may overlap. Generally the probability values which indicated to which category a subject belonged were not correlated with the severity of the disorders but two schizophrenic patients which appeared to have relatively low sum of scores for the symptoms related to schizophrenia (their scores for symptoms were 8 and 9) did also have a relatively low probabilities of being schizophrenic (probabilities of them being schizophrenic were 0.58 and 0.46 respectively).

The second method of identifying the schizophrenic, PD and HD patients from normal subjects was a novel method of extracting CNV features in the time domain and using the features in neural networks. During the training mode the neural networks always successfully identified all the patients from the three categories from normal subjects. The success rates achieved during the test mode of the neural networks were:

- When differentiating between HD patients and normal subjects all HD patients (100%) and all normal subjects (100%) were correctly identified.
- When differentiating between schizophrenic patients and normal subjects all but one of the patients (90%) and all the normal subjects (100%) were

correctly classified.

- When differentiating between PD patients and normal subjects, all PD patients (100%) and all but one of the normal subjects (93.75%) were correctly identified.

The schizophrenic patient misclassified by the frequency analysis and discriminant analysis of the CNV was classified correctly by the neural network method, and the schizophrenic patient misclassified by the neural network method was classified correctly be the frequency analysis and discriminant analysis method. A similar finding was observed when differentiating between PD patients and normal subjects ie. the PD patient misclassified by the neural network method was classified correctly by the frequency analysis and discriminant analysis method. These observations suggest that the amalgamation of the two techniques may further increase the success rate of identifying the patients.

The third method of identifying the schizophrenic, PD, and HD patients involved the application of principal components analysis and cluster analysis to the CNV waveforms. The CNV features used in this method of identifying patients were the same as those used in neural networks. This method was not as effective as the other two methods of identifying the schizophrenic, PD and HD patients. This method was also applied to 21 at-risk of HD patients and it resulted in identifying 7 at-risk of HD patients as abnormal at-risk of HD patients. As it is established that the CNV in known HD patients is abnormal (references were given in the introduction chapter) therefore it was suggested that these 7 abnormal at-risk of HD patients would develop HD. These results then led to analysing the CNV amplitude in the 7 abnormal and the remaining 14 at-risk of HD patients. It was shown that the CNV amplitude in the 7 abnormal at-risk of HD patients was significantly different from those in their normal control subjects ($p < 0.001$,

df=12). The CNV amplitude in the remaining 14 at-risk of HD patients was not significantly different from the CNV amplitude in normal control subjects.

The reaction time analysis of the schizophrenic, PD, and HD patients indicated that the reaction times in all three patient categories are significantly different from the reaction times in their normal control subjects and therefore these results indicate that the brain structural abnormalities observed in the above named patients can alter the patients' motor response to stimuli. The reaction time analysis of the at-risk of the HD patients indicated that the reaction time in the 7 abnormal at-risk of HD patients (these were identified as abnormal using principal components analysis and cluster analysis) is significantly different from the reaction time in normal control subjects ($p<0.05$, $df=12$). The reaction time of the remaining 14 at-risk of HD patients were not significantly different from the reaction time of their normal control subjects. These results were in agreement with the results obtained when the CNV amplitude was analysed in the at-risk of HD patients. The results obtained involving the application of principal components analysis and cluster analysis, and following findings related to the CNV amplitude analysis and reaction time analysis in the at-risk of HD patients are indicative that the structural brain abnormalities observed in the HD patients may start to develop well prior to the onset of the disease causing changes in the CNV and reaction time.

Overall, three different methods of identifying schizophrenic, PD and HD patients were successfully implemented during the course of the project. The method which involved the use of neural networks was considered to be the more suitable for use by neurophysiologists and psychiatrists as its implementation does not require a detailed knowledge of signal processing.

Since identification of the 7 abnormal at-risk of HD patients, one of the 7 abnormal at-risk of HD patients has developed HD and non of the 14 normal at-risk of HD patients have developed HD.

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Appendices

Appendix A Listing of Data Recording Programs

```
PROGRAM DATA_ACQUISITION (INPUT, OUTPUT, DATA_FILE);

{Program name = ACQ.PAS

This program initialises the DT2805 board used for its programmable gain
amplifier and analogue to digital convertor. It then obtains the recording
parameters.

The program is linked to the assembly language program SAMPLE1.ASM which
acquires the signals from 8 channels and stores them on the hard disk of
the PC.

During the execution of this program a menu appears and the operator is
asked for an entry. The list of options available is described in chapter 4.}

{global parameters}

CONST
        {DT2805 board addresses}
        BASE_ADDRESS     = $2EC; {base address}
        COMMAND_REGISTER = $2ED; {command register address}
        STATUS_REGISTER  = $2ED; {status register address}
        DATA_REGISTER    = BASE_ADDRESS; {data register address}

        {Bit position of DT2805 board status register}
        COMMAND_WAIT = $4; {ready bit}
        WRITE_WAIT   = $2; {data in full bit}
        READ_WAIT    = $1; {data out ready bit}

        {PC warning to indicate experiment is over}
        HZ = 200; {frequency of the sound}
        US = 1000; {duration of the sound}

        {cursor initial positions on the VDU of the PC}
        X = 5; {x axis}
        Y = 5; {y axis}

{-------------------------------------------------}

TYPE
        NAME = STRING [12];

{-------------------------------------------------}

VAR
        STATUS, TEMP, RESULT, VALUE, TRIAL : INTEGER;
        PRE_CNV, CNV, POST_CNV : INTEGER;
        ORG_FILE : FILE OF INTEGER;
        CHECK, OK, EXISTS, TRY_AGAIN, RUN : BOOLEAN;
        DECISION : CHAR;
        DISK_FILE, PAT_NAME : NAME;
```

```
        DATA_FILE : TEXT;
{-------------------------------------------------}

LABEL EXIT;

{-------------------------------------------------}

{the external assembly language program definition}

PROCEDURE SAMPLE (PRE_CNV,CNV,POST_CNV,TRIAL : INTEGER);
EXTERNAL'SAMPLE1.BIN';


{-------------------------------------------------}

PROCEDURE LEGAL_STATUS (VAR ERROR :BOOLEAN);

{Check the status register of the DT2805 board}

CONST
        FATAL_ERROR = $70; {code for examining possible error}

BEGIN
        STATUS := PORT[STATUS_REGISTER];
        IF NOT ((STATUS AND FATAL_ERROR) = 0) THEN
        BEGIN
        ERROR := FALSE;
        WRITELN ('Fatal error, run aborted.');
        END
        ELSE ERROR := TRUE;
END; {procedure legal status}


{-------------------------------------------------}

PROCEDURE WAIT_SET (SBIT : INTEGER);

{Procedure to wait for the specified bit/s to be set}

VAR
        BIT_SET : BOOLEAN;

BEGIN
        BIT_SET := FALSE;
        REPEAT
        STATUS := PORT[STATUS_REGISTER];
        RESULT := (STATUS AND SBIT);
        IF (RESULT = SBIT) THEN
        BIT_SET := TRUE;
        UNTIL BIT_SET;
END; {Procedure bit set}


{-------------------------------------------------}

PROCEDURE WAIT_CLEAR (CBIT : INTEGER);
```

```
{procedure to wait until the specified bit is cleared}

VAR
        BIT_CLEAR : BOOLEAN;

BEGIN
        BIT_CLEAR := FALSE;
        REPEAT
        STATUS := PORT[STATUS_REGISTER];
        RESULT := (STATUS AND CBIT) XOR CBIT;
        IF (RESULT = CBIT) THEN
        BIT_CLEAR := TRUE;
        UNTIL BIT_CLEAR;
END; {procedure wait clear}


{-------------------------------------------------}

PROCEDURE CHECK_ERROR(VAR CHECK : BOOLEAN);

{procedure to check for error after an operation}

CONST
        ERROR_BIT = $80; {DT2805 board operation check code}

BEGIN
        WAIT_CLEAR(WRITE_WAIT);
        WAIT_SET(COMMAND_WAIT);
        STATUS := PORT[STATUS_REGISTER];
        IF (STATUS AND ERROR_BIT) = 0 THEN
        CHECK := TRUE
        ELSE CHECK := FALSE;
END; {procedure operation check error}


{-------------------------------------------------}

PROCEDURE RESET_BOARD;

{procedure to reset the DT2805 board}

CONST
        CSTOP  = $F; {stop command code}
        CCLEAR = $1; {clear command code}

BEGIN
        PORT [COMMAND_REGISTER] := CSTOP;
        TEMP := PORT [DATA_REGISTER];
        WAIT_CLEAR (WRITE_WAIT);
        WAIT_SET (COMMAND_WAIT);
        PORT [COMMAND_REGISTER] := CCLEAR;
END; {Procedure reset}


{-------------------------------------------------}

FUNCTION EXIST (FILE_NAME : NAME) : BOOLEAN;
```

```
{function to safeguard the files on hard disk}

VAR
        OLD_FILE  : FILE;

BEGIN
        ASSIGN (OLD_FILE, FILE_NAME);
        {$I-} {disable error handler}
        RESET (OLD_FILE);
        {SI+} {enable error handler}
        EXIST :=(IORESULT =0); {if file exist, exists = true}
END; {exist function}


{-------------------------------------------------}

PROCEDURE DELETE_FILE (FILE_NAME : NAME);

{procedure to delete a file}

VAR
        OLD_FILE : FILE;

BEGIN
        ASSIGN (OLD_FILE, FILE_NAME);
        CLOSE (OLD_FILE);
        ERASE (OLD_FILE);
END; {procedure delete file}


{-------------------------------------------------}

PROCEDURE USER_INPUT (VAR
                PRE_CNV, CNV, POST_CNV, TRIAL : INTEGER;
                VAR PAT_NAME : NAME;
                VAR RUN : BOOLEAN);

{this procedure asks the user for the recording parameters}

VAR
        REPLY, DEL : CHAR;
        READY : BOOLEAN;

BEGIN
        READY := FALSE;
        CLRSCR;

        REPEAT
                GOTOXY (X,Y);

                WRITELN ('        DATA RECORDING ROUTINE');
                GOTOXY (X,Y+3);
                WRITE ('****************************************');
                WRITELN ('******************');
                GOTOXY (X,Y+5);
                WRITE ('Please reply to the followings, ');
```

```
        WRITELN ('Enter an integer number :-');
REPEAT
                GOTOXY (X,Y+7);
                WRITE ('Pre-warning-stimulus recording time');
                WRITE (', Enter "1" to "6" seconds :  ');
                READLN (PRE_CNV);
UNTIL (PRE_CNV > 0) AND (PRE_CNV <= 6);

REPEAT
        GOTOXY (X,Y+9);
        WRITE ('ISI recording time, ');
        WRITE ('Enter "1" to "3" seconds :  ');
        READLN (CNV);
UNTIL (CNV > 0) AND (CNV <= 3);

REPEAT
        GOTOXY (X,Y+11);
        WRITE ('Post-imperative-stimulus time, ');
        WRITE ('Enter "1" to "12" seconds :  ');
        READLN (POST_CNV);
UNTIL (POST_CNV > 0) AND (POST_CNV <= 12);

REPEAT
        GOTOXY (X,Y+13);
        WRITE ('Number of trials required, ');
        WRITE ('Enter "1" to "32" :  ');
        READLN (TRIAL);
UNTIL (TRIAL > 0) AND (TRIAL <= 32);

GOTOXY (X,Y+15);
WRITE ('*****************************************');
WRITELN ('******************');

GOTOXY (X,Y+17);
WRITELN ('Do you wish to reenter above data ? ');
GOTOXY (X,Y+19);
WRITE ('If so type in "Y", if not type "N"  ');
READLN (REPLY);

IF (REPLY = 'N') OR (REPLY = 'n') THEN
READY := TRUE;
IF (REPLY = 'Y') OR (REPLY = 'y') THEN
CLRSCR;

IF (REPLY = 'N') OR (REPLY = 'n') THEN
IF (PRE_CNV + CNV + POST_CNV) > 12 THEN
BEGIN
        CLRSCR;
        READY := FALSE;
        GOTOXY (X,Y-2);
        WRITE ('The CNV paradigm should not exceed');
        WRITE (' 12 seconds');
END;

UNTIL READY = TRUE;

CLRSCR;
```

```
        READY := FALSE;
        REPEAT
                GOTOXY (X,Y);
                WRITE ('*****************************************');
                WRITELN ('**********');
                GOTOXY (X,Y+2);
                WRITELN ('Please enter the data file name ');
                WRITE ('    in this format : NNNNNNNN.DAT ');
                READLN (PAT_NAME);

                GOTOXY (X,Y+5);
                WRITE ('*****************************************');
                WRITELN ('**********');
                GOTOXY (X,Y+7);
                WRITELN ('Do you wish change the above name ?');
                WRITE ('    If no enter "N", else enter RET key ');
                READLN (REPLY);
                IF (REPLY = 'N') OR (REPLY = 'n') THEN
                READY :=TRUE;

                {Check if a file with similar name already exists}
                RUN := TRUE;
                EXISTS := EXIST (PAT_NAME);
                IF EXISTS THEN
                BEGIN
                        GOTOXY (X,Y+11);
                        WRITELN ('Above file already exists !');
                        GOTOXY (X,Y+12);
                        WRITELN ('Do you wish to delete it ?');
                        GOTOXY (X,Y+13);
                        WRITE ('If so enter "Y", otherwise "N" : ');
                        READLN (DEL);

                        IF (DEL = 'Y') OR (DEL = 'y') THEN
                        BEGIN
                        WRITELN ('File ',PAT_NAME,' is deleted');
                        DELETE_FILE (PAT_NAME)
                END
        ELSE
        BEGIN
                GOTOXY (X,Y);
                CLRSCR;
                WRITELN ('Run aborted as file exists');
                RUN := FALSE;
                END;
        END;

        CLRSCR;
         UNTIL READY = TRUE;

END;

{-----------------------------------------------}
```

```
PROCEDURE SUB_FILE;

{procedure to form a file containing only a specified trial}

CONST
        BASE_FACTOR = 4096; {2 to the power 12}
        RANGE       = 20;  {range of input signals, -10 to +10}
        MAX_VOLTAGE = 10;  {maximum input voltage allowed}
        SAMPLE_RATE = 125; {sampling rate}
        MIC_SCALE   = 200; {microvolt scale}
        MIL_SCALE   = 4000; {millivolt scale}

VAR
        NO1, NO2, NUMBER, AD_GAIN, CHANNEL, TRI_SEL :
        INTEGER;
        FACTOR, RESOLUTION, BI_VOLT, I, N : REAL;
        DURATION, N1, N2, TIME : REAL;
        COMP_OUTPUT, ELEMENT1, ELEMENT2, DECISION : CHAR;
        OLD_FILE, NEW_FILE : STRING [12];
        SUB_FILE, DATA_FILE : TEXT;
        CHECK : BOOLEAN;

BEGIN
        CHECK :=FALSE;
        CLRSCR;
        REPEAT
                GOTOXY (X,Y);
                WRITELN ('************************************');
                GOTOXY (X,Y+1);
                WRITELN ('      Sub_file   Routine');
                GOTOXY (X,Y+2);
                WRITELN ('************************************');
                GOTOXY (X,Y+4);

                WRITELN ('Routine to form a sub_file.');
                GOTOXY (X,Y+5);
                WRITE ('This file will contain the data from ');
                WRITELN ('one trial of the experiment.');

                GOTOXY (X,Y+8);
                WRITELN ('Please enter the followings:');
                GOTOXY (X,Y+10);
                WRITE ('The main file name  : ');
                READLN (OLD_FILE);
                GOTOXY (X,Y+11);
                WRITE ('The sub_file name  : ');
                READLN (NEW_FILE);
                GOTOXY (X,Y+12);
                WRITE ('The trial number selected  : ');
                READLN (TRI_SEL);
                GOTOXY (X,Y+13);
                WRITE ('The duration of the trial in seconds  : ');
                READLN (DURATION);

                GOTOXY (X,Y+15);
                WRITE ('If you wish to re_enter above data, ');
                WRITELN ('enter "Y"');
```

```
        GOTOXY (X,Y+16);
        WRITE ('Otherwise enter "N"  : ');
        READLN (DECISION);
        IF (DECISION = 'N') OR (DECISION = 'n') THEN
        CHECK := TRUE;
        CLRSCR;
UNTIL CHECK = TRUE;

GOTOXY (X,Y);
WRITELN ('**********************');
GOTOXY (X,Y+2);
WRITELN ('Please wait .....');
GOTOXY (X,Y+4);
WRITELN ('**********************');

ASSIGN (DATA_FILE, OLD_FILE);
RESET (DATA_FILE);
ASSIGN (SUB_FILE, NEW_FILE);
REWRITE (SUB_FILE);

N := (TRI_SEL -1) * (SAMPLE_RATE * DURATION);
RESOLUTION := RANGE / BASE_FACTOR;
I :=1;
WHILE (I-1) < N DO
        BEGIN
                FOR CHANNEL := 1 TO 8 DO
                        READ (DATA_FILE, COMP_OUTPUT,
                        ELEMENT1,
                        ELEMENT2);
                I := I +1;
        END;

N2 := SAMPLE_RATE * DURATION;
1 := 0;
REPEAT
        TIME := N1 / SAMPLE_RATE;
        WRITE (SUB_FILE, TIME:3:5,'   ');
        N1 := N1 +1;

        FOR CHANNEL := 1 TO 8 DO
        BEGIN
                READ (DATA_FILE, COMP_OUTPUT, ELEMENT1,
                        ELEMENT2);
                NO1 := ORD(ELEMENT1);
                NO2 := ORD(ELEMENT2);
                NUMBER := NO1 + (NO2 * 256);
                FACTOR := RESOLUTION * NUMBER;

                CASE ORD (COMP_OUTPUT) OF
                        0 : AD_GAIN := 1;
                        1 : AD_GAIN := 10;
                        2 : AD_GAIN := 100;
                        3 : AD_GAIN := 500;
                END; {case}

                BI_VOLT := (FACTOR - MAX_VOLTAGE) /
                AD_GAIN;
```

```
                IF CHANNEL < 7 THEN
                BI_VOLT := BI_VOLT * MIC_SCALE
                ELSE
                BI_VOLT := BI_VOLT * MIL_SCALE;
                WRITE (SUB_FILE, BI_VOLT:6:6,'    ');

        END; {for}
        WRITELN (SUB_FILE);

        UNTIL N1 = N2;

        CLOSE (DATA_FILE);
        CLOSE (SUB_FILE);

END; {procedure sub_file}


{-------------------------------------------------}

PROCEDURE RESPONSE_TIMES;

{procedure to display the reaction times in the record}

CONST
        SAMPLE_RATE = 125; {sample_rate}

VAR
        INDEX, TRIAL, NO1, NO2, CHANNEL, N : INTEGER;
        TIME, SAMPLES, K, DURATION, AVERAGE_RT : REAL;
        FILE_NAME, RESP_FILE_NAME : STRING [12];
        DATA_FILE, RESPONSE_FILE : TEXT;
        ELEMENT1, ELEMENT2, DECISION, RESPONSE, A : CHAR;
        CHECK : BOOLEAN;

BEGIN
        CHECK := FALSE;
        AVERAGE_RT := 0;
        CLRSCR;
        REPEAT
                GOTOXY (X,Y);
                WRITELN ('          Reaction  Time  Routine');
                GOTOXY (X,Y+3);
                WRITE
('=================================');
                WRITELN ('==========');
                GOTOXY (X,Y+4);
                WRITELN ('Routine to display the reaction times');
                GOTOXY (X,Y+5);
                WRITE
('=================================');
                WRITELN ('==========');

                GOTOXY (X,Y+7);
                WRITE ('Please enter the filename :  ');
                READLN (FILE_NAME);
                GOTOXY (X,Y+9);
```

```
        WRITE ('The number of trials in the record :  ');
        READLN (TRIAL);
        GOTOXY (X,Y+11);
        WRITE ('The trial duration :  ');
        READLN (DURATION);
        GOTOXY (X,Y+13);
        WRITE ('For a reaction time file enter "Y", ');
        WRITE ('otherwise enter "N" :  ');
        READLN (RESPONSE);
        IF (RESPONSE = 'Y') OR (RESPONSE = 'y') THEN
        BEGIN
                GOTOXY (X,Y+15);
                WRITE ('The reaction time filename :  ');
                READLN (RESP_FILE_NAME);
        END;

        GOTOXY (X,Y+17);
        WRITE ('To re_enter the above data, enter "Y", ');
        WRITE ('otherwise enter "N" :  ');
        READLN (DECISION);
        IF (DECISION = 'N') OR (DECISION = 'n') THEN
        CHECK := TRUE;
        CLRSCR;

UNTIL CHECK = TRUE;

IF (RESPONSE = 'Y') OR (RESPONSE = 'y') THEN
BEGIN
        ASSIGN (RESPONSE_FILE, RESP_FILE_NAME);
        REWRITE (RESPONSE_FILE);
END;

WRITELN('Patients reaction times are :');
WRITELN;
WRITELN('|==========================|');
WRITELN('|  Trial Number | Time (Seconds) |');
WRITELN('|===============|================|');

ASSIGN (DATA_FILE, FILE_NAME);
RESET (DATA_FILE);

SAMPLES := 0;
{skip the CNV data}
K := (DURATION * SAMPLE_RATE * TRIAL);
REPEAT
        FOR N := 1 TO N DO
        READ (DATA_FILE, A);
        SAMPLES := SAMPLES + 1;
UNTIL SAMPLES = K;

FOR INDEX := 1 TO TRIAL DO
BEGIN
        READ (DATA_FILE, ELEMENT1, ELEMENT2);
        NO1 := ORD(ELEMENT1);
        NO2 := ORD(ELEMENT2);
        TIME := NO1 + (NO2 * 256);
```

```
                TIME :=TIME / 1000;
                AVERAGE_RT := AVERAGE_RT + TIME;

                WRITELN('|       ',INDEX:2,'       |',' '
                        ,TIME:1:3,'      |');
                WRITELN('|-----------------------------|');

                IF (RESPONSE = 'Y') OR (RESPONSE = 'y') THEN
                WRITELN (RESPONSE_FILE, INDEX:2,'       ',
                        TIME:1:3);

        END;

        AVERAGE_RT := AVERAGE_RT / TRIAL;
        WRITELN;
        WRITELN;
        WRITE ('Average RT based on ',trial,' ','trials is ');
        WRITELN (average_rt:5:3);
        CLOSE (DATA_FILE);
        IF (RESPONSE = 'Y') OR (RESPONSE = 'y') THEN
        CLOSE (RESPONSE_FILE);

END; {procedure response_time}


{-------------------------------------------------}

{main section}
BEGIN
        TRY_AGAIN := FALSE;
        REPEAT
                CLRSCR;
                GOTOXY (X,Y);
                WRITELN ('      DATA  ACQUISITION  PROGRAM');
                GOTOXY (X,Y+1);
                WRITELN('=========================');

                GOTOXY (X,Y+4);
                WRITE ('************************************');
                WRITELN ('*****************');
                GOTOXY (X,Y+5);
                WRITE ('*                                  ');
                WRITELN ('            *');
                GOTOXY (X, Y+6);
                WRITE ('* Please enter :  "F" to FAMILIARISE');
                WRITELN ('               *');
                GOTOXY (X,Y+7);
                WRITE ('*              "P" to PRACTICE the ');
                WRITELN ('experiment       *');
                GOTOXY (X,Y+8);
                WRITE ('*              "R" to RECORD data ');
                WRITELN ('              *');
                GOTOXY (X,Y+9);
                WRITE ('*              "S" to form a SUB_FILE');
                WRITELN (' form main file *');
                GOTOXY (X,Y+10);
                WRITE ('*              "T" to display the');
```

```
        WRITELN (' response TIMES     *');
        GOTOXY (X,Y+11);
        WRITE ('*               "Q" to QUIT');
        WRITELN ('                      *');
        GOTOXY (X,Y+12);
        WRITE ('*                       ');
        WRITELN ('                       *');
        GOTOXY (X,Y+13);
        WRITE ('*****************************************');
        WRITELN ('*****************');

        GOTOXY (X, Y+16);
        WRITE ('Decision please  > ');
        READ (DECISION);

        IF (DECISION = 'F') OR (DECISION = 'f')
        OR (DECISION = 'P') OR (DECISION = 'p') THEN

BEGIN
        {check for legal status register condition}
        LEGAL_STATUS (OK);
        IF NOT OK THEN
        GOTO EXIT;

        {reset the DT2805 board}
        RESET_BOARD;

        CLRSCR;
        GOTOXY (X+3,Y+4);
        WRITELN ('*****************');
        GOTOXY (X+3,Y+6);
        WRITELN('Please wait .....');
        GOTOXY (X+3,Y+8);
        WRITELN ('*****************');

        IF (DECISION = 'F') OR (DECISION = 'f') THEN
        SAMPLE (1, 1, 10, 5);

        IF (DECISION = 'P') OR (DECISION = 'p') THEN
        SAMPLE (1, 1, 10, 15);

        CLRSCR;
        GOTOXY (X+5,Y);
        WRITELN ('*******************');
        GOTOXY (X+5, Y+2);

        WRITELN('The end of practice ');
        GOTOXY (X+5,Y+4);
        WRITELN ('*******************');

        TEMP:= 0;
        REPEAT
                SOUND (HZ);
                DELAY (US);
                NOSOUND;
                TEMP := TEMP+1;
        UNTIL  TEMP = 2;
```

```
        {delete the test file}
        DISK_FILE := 'CNVAMP.DAT';
        DELETE_FILE (DISK_FILE);

END; {if}


IF (DECISION = 'R') OR (DECISION = 'r') THEN

BEGIN
        {check for legal status register condition}
        LEGAL_STATUS(OK);
        IF NOT OK THEN
        GOTO EXIT;

 {reset the DT2805 board}
        RESET_BOARD;

        {get user input}
        USER_INPUT (PRE_CNV, CNV, POST_CNV, TRIAL,
              PAT_NAME, RUN);
        IF RUN = FALSE THEN
        GOTO EXIT;

        CLRSCR;
        GOTOXY (X+3,Y+4);
        WRITE ('************************************');
        WRITELN ('***********');
        GOTOXY (X+3,Y+6);
        WRITE ('Signal is being recorded. ');
        WRITELN('   Please wait .....');
        GOTOXY (X+3,Y+8);
        WRITE ('************************************');
        WRITELN ('***********');
        {call assembly language procedure}
        SAMPLE (PRE_CNV, CNV, POST_CNV, TRIAL);

        CLRSCR;
        GOTOXY (X+5,Y);
        WRITELN ('*************************');
        GOTOXY (X+5, Y+2);

        WRITELN('The signal is recorded ');
        GOTOXY (X+5,Y+4);
        WRITELN ('*************************');

        SOUND (HZ);
        DELAY (US);
        NOSOUND;

        {rename the file}
        DISK_FILE := 'CNVAMP.DAT';
        ASSIGN (ORG_FILE, DISK_FILE);
        RENAME (ORG_FILE, PAT_NAME);

END; {recording}
```

```
        IF (DECISION = 'S') OR (DECISION = 's') THEN
        SUB_FILE;

        IF (DECISION = 'T') OR (DECISION = 't') THEN
        RESPONSE_TIMES;

        IF (DECISION = 'Q') OR (DECISION = 'q') THEN
        GOTO EXIT;
        WRITELN;
        WRITE ('If you wish another go, enter "Y"');
        WRITE (' otherwise enter "N"  : > ');
        READLN (DECISION);
        IF (DECISION = 'N') OR (DECISION = 'n') THEN
        TRY_AGAIN : = TRUE;

        UNTIL TRY_AGAIN =TRUE;
EXIT:

END.
```

```
TITLE SAMPLE1

;-----------------------------------------------------------------
;| Procedure to sample the signals and to store the data         |
;| on the hard disk of the PC. The signals are acquired          |
;| from 8-analogue channels. The output of the multiplexer       |
;| is connected to a window detector and a programmable          |
;| gain amplifier (PGA). The function of the window              |
;| detector is to determine the gain setting for the PGA.        |
;| The output of the PGA is connected to a 12-bit analogue       |
;| to digital converter (A/D). The PGA and the A/D are on        |
;| the DT2805 board.                                             |
;|                                                               |
;|                                                               |
;| The timing and sampling signals are provided by two           |
;| programmable interval timers. The digital interfacing         |
;| is achieved using a programmable parallel port device.        |
;| Assembly language : 80286                                     |
;| Program name      : SAMPLE1.ASM                               |
;| This program is called from ACQ.PAS Pascal Program.           |
;|                                                               |
;|                                                               |
;| Registers used : AX, BX, CX, DX, CS, DS, DI, SI and BP.       |
;| Ports used : The digital ports A, B, and C of 8255A-5.        |
;|                                                               |
;| Parameters received : Number of trials and CNV paradigm.      |
;| Parameters returned : None.                                   |
;-----------------------------------------------------------------

;.............
; Constants .
;.............

; DT2805 board addresses
DTBADDR     EQU  02ECH          ;Base address
DATARG      EQU  DTBADDR        ;Data register
STCDRG      EQU  DTBADDR+1      ;Status/Command register

ADMODE      EQU  0CH            ;A/D command mode

; DT2805 board status register bit position
DOUTRDY     EQU  01H            ;Data out ready bit
DINFULL     EQU  02H            ;Data in full bit
RDYBIT      EQU  04H            ;Ready bit

; DT2805 multiplexing channel
CHANNEL     EQU  00H            ;Channel zero

; 8259 interrupt controllers #1 port addresses
; Controller #1
INTA00      EQU  20H
INTA01      EQU  21H
EOI         EQU  20H            ;End of interrupt command
```

```
; 8254 counter/timer #1 addresses, external
COUNTR0     EQU  300H        ;Counter 0
COUNTR1     EQU  302H        ;Counter 1
COUNTR2     EQU  304H        ;Counter 2
CONTREG     EQU  306H        ;Common control register

; 8253 counter/timer #2 address, external
PTM2CR0     EQU  310H        ;Counter 0
PTM2CR1     EQU  312H        ;Counter 1
PTM2CR2     EQU  314H        ;Counter 2
PTM2CRG     EQU  316H        ;Common control register

; 8255A_5 programmable parallel ports
PORTA       EQU  308H        ;Port A
PORTB       EQU  30AH        ;Port B
PORTC       EQU  30CH        ;Port C
CONREG      EQU  30EH        ;Control register

; Maximum number of input channels
MAXCHN      EQU  08H         ;8 channel differential

; Codes for DOS function calls
CREFILE     EQU  3CH         ;Create file code
FILEATR     EQU  00H         ;File attribute code
WRCODE      EQU  40H         ;Write code
CLOSFIL     EQU  3EH         ;Close file code
OPENFIL     EQU  3DH         ;Open file code
ACCODE      EQU  82H         ;Access file code

; Addresses where the A/D output is stored
ADSEG       EQU  3000H       ;Segment
ADOFFST     EQU  0001H       ;Offset
RESPTME     EQU  65400       ;Reaction time location

EOI         EQU  020H        ;End of interrupt command
SAMPRT      EQU  125         ;Sampling rate

;==========================================================


;           Code Segment
;           ------------

CODE        SEGMENT BYTE
            ASSUME CS:CODE          ;Initialise code seg. reg.

; PROCEDURE SAMPLE (PAGES : INTEGER);

SAMPLE      PROC     NEAR       ;Define the procedure
            PUSH     BP         ;Save bp register
            MOV      BP,SP      ;Initialise bp with sp

; Get the starting address of the procedure
```

```
                PUSH    AX          ;Save ax reg.
                CALL    START       ;Put IP on stack
START:          POP     AX          ;Transfer IP into ax
                SUB     AX,7        ;Get proc. starting addr.
                JMP     CONT        ;Skip the variable section

;=============================================

;.............
; Variables .
;.............
CNVFILE  DB "C:CNVAMP.DAT",0        ;CNV file name
NETPATH  DB 'C:CNVAMP.DAT',0        ;CNV file network path
GCODE    DB ?                       ;Gain code
CHNNO    DB ?                       ;Channel number
FLAG     DB ?                       ;Error flag

STARTAD  DW ?                       ;Proc. starting address
RANDNO   DW ?                       ;Random no. for ITI
FILEHDL  DW ?                       ;File handle of file
TRIAL    DW ?                       ;Number of trials
TRIALST  DW ?                       ;Trials recorded
POSTCNV  DW ?                       ;Post-imperative-sti. time
CNV      DW ?                       ;ISI time
PRECNV   DW ?                       ;Pre-warning-sti. time
SAMPNO   DW ?                       ;Sample number
DIREG    DW ?                       ;Byte counter
RESPTR   DW ?                       ;Reaction time byte pointer
BYTESUM  DW ?                       ;Total no. of bytes/trial

;=============================================


; Save the starting addr. of proc. & the contents of regs.
CONT:   MOV     STARTAD,AX          ;Starting addr. of proc.
        PUSH    BX                  ;Registers used
        PUSH    CX
        PUSH    DX
        PUSH    DS
        PUSH    DI
        PUSH    SI

        JMP     ENDISR              ;Go to start of proc.
```

```
;=====================================

; Sampling interrupt service routine
ISRSAM      PROC FAR
            CLI
            PUSH DX                 ;Save the registers
            PUSH BX
            PUSH DX
            MOV  AL,EOI             ;Enable interrupt
            OUT  INTA00,AL

            MOV  CHNNO,0            ;Set the staring channel
            ADD  SAMPNO,1           ;Update sample number

            MOV  DI,DIREG           ;Initialise byte pointer
;.....................................................

; Switch the multiplexer to the required channel
; (The multiplexer address lines are connected to
; port A: bits 0, 1, 2 & 3 )
NEXTCH      MOV  DX,PORTA           ;Get port A address
            IN   AL,DX              ;Read port A
            AND  AL,11110000B       ;Set 1st 4 bits to 0
            OR   AL,CHNNO           ;Set the channel number
            OUT  DX,AL              ;Write the bit pattern
;.....................................................

; Provide delay for the window detector to settle
            MOV  BL,3
DELAY:      DEC  BL
            JNZ  DELAY

;.....................................................

; Read the window detector output
; (the window detector output is connected to port B
;  bits 0, 1, & 2)
            MOV  DX,PORTB           ;Get port B address
            IN   AL,DX              ;Read port B
            AND  AL,00000111B       ;Mask out unwanted bits

;.....................................................

; Determine & store gain code from the window detector
            MOV  BL,0               ;Determine gain code
            SHR  AL,1
            JNC  ADD1
            INC  BL
ADD1:       SHR  AL,1
            ADC  AL,BL

            MOV  ES:[DI],AL         ;Store the gain code
            MOV  AH,AL

            INC  DI                 ;Update byte counter

;.....................................................
```

```
; Set DT2805 board A/D parameters
; A/D mode
                MOV  DX,STCDRG      ;Get status reg. address
WAITAD:         IN   AL,DX          ;Repeat : read status reg.
                AND  AL,RDYBIT      ; Check the ready bit
                JZ   WAITAD         ;Until ready bit is high
                MOV  AL,ADMODE      ;Get command mode
                OUT  DX,AL          ;Output to command reg.

; Gain code
WAITG:          IN   AL,DX          ;Repeat : read status reg.
                AND  AL,DINFULL     ; Check data in full bit
                JNZ  WAITG          ;Until data in full is low

                MOV  DX,DATARG      ;Get data reg. address
                MOV  AL,ah          ;Get the gain code
                OUT  DX,AL          ;Write it to data reg.

; Channel number
                MOV  X,STCDRG       ;Get status reg. addr.
WAITC:          IN   AL,DX          ;Repeat : read status reg.
                AND  AL,DINFULL     ;Check data in full bit
                JNZ  WAITC          ;Until data in full is low

                MOV  DX,DATARG      ;Get data reg. address
                MOV  AL,CHANNEL     ;Get channel number
                OUT  DX,AL          ;Write it to data reg.

;.....

; Read & store A/D output
; Low byte
                MOV  DX,STCDRG      ;Get status reg. address
WAITL:          IN   AL,DX          ;Repeat : read status reg.
                AND  AL,DOUTRD      ; Check data out ready bit
                JZ   WAITL          ;Until data out ready high
                MOV  DX,DATARG      ;Get data register address
                IN   AL,DX          ;Read low byte of A/D
                MOV  AH,AL          ;Store the value in AH reg.

; High byte
                MOV  DX,STCDRG      ;Get status reg. address
WAITH:          IN   AL,DX          ;Repeat : read status reg.
                AND  AL,DOUTRDY     ; Check data out ready bit
                JZ   WAITH          ;Until data out ready high
                MOV  DX,DATARG      ;Get data register address
                IN   AL,DX          ;Read high byte of A/D
                XCHG AH,AL          ;Store high byte in AH reg.

; Store the A/D output
                MOV  ES:[DI],AL     ;Store the low byte
                INC  DI
                MOV  ES:[DI],AH     ;Store the high byte
                INC  DI

;.....
```

```
; Switch multiplexer to next channel
                INC   CHNNO             ;Update channel number
                MOV   DX,PORTA          ;Get part A address
                IN    AL,DX             ;Read port A
                AND   AL,11110000B      ;Mask 4 LSBs
                OR    AL,CHNNO          ;Set the channel number
                OUT   DX,AL             ;Write the bit pattern
;.....

; Provide delay for the window detector to settle
                MOV   BL,3
DELAY2:         DE    BL
                JNZ   DELAY2

;.....

; Read window detector
;
                MOV   DX,PORTB          ;Get port B address
                IN    AL,DX             ;Read port B
                AND   AL,00000111B      ;Mask unwanted bits

;.....
; Determine and store the gain code
                MOV   BL,0
                SHR   AL,1
                JNC   ADD2
                INC   BL
ADD2:           SHR   AL,1
                ADC   AL,BL

                MOV   ES:[DI],AL        ;Store the gain code
                MOV   AH,AL
                INC   DI                ;Update byte counter

;.....

; Set DT2805 board parameters
; A/D mode
                MOV   DX,STCDRG         ;Get status reg. address
WAITA2:         IN    AL,DX             ;Repeat : read status reg.
                AND   AL,RDYBIT         ; Check ready bit
                JZ    WAITA2            ;Until ready bit is high
                MOV   AL,ADMODE         ;Get command mode
                OUT   DX,AL             ;Output to command reg.

; Gain code
WAITG2:         IN    AL,DX             ;Repeat : read status reg.
                AND   AL,DINFULL        ; Check data in full bit
                JNZ   WAITG2            ;Until it is low
                MOV   DX,DATARG         ;Get data reg. address
                MOV   AL,AH             ;Get gain code
                OUT   DX,AL             ;Write to data register

;Channel number
                MOV   DX,STCDRG         ;Get status reg. address
```

```
WAITC2:     IN    AL,DX          ;Repeat : read status reg.
            AND   AL,DINFULL     ; Check data in full bit
            JNZ   WAITC2         ;Until it is low
            MOV   DX,DATARG      ;Get data reg. address
            MOV   AL,CHANNEL     ;Get channel number
            OUT   DX,AL          ;Write it into data reg.
;.....

;Read & store A/D output
; Low byte
            MOV   DX,STCDRG      ;Get status reg. address
WAITL2:     IN    AL,DX          ;Repeat : read status reg.
            AND   AL,DOUTRDY     ; Check data out ready bit
            JZ    WAITL2         ;Until it is high
            MOV   DX,DATARG      ;Get data reg. address
            IN    AL,DX          ;Read low byte of A/D
            MOV   AH,AL          ;Store it in AH register

; High byte
            MOV   DX,STCDRG      ;Get status reg. address
WAITH2:     IN    AL,DX          ;Repeat : read status reg.
            AND   AL,DOUTRDY     ; Check data out ready bit
            JZ    WAITH2         ;Until it is high
            MOV   DX,DATARG      ;Get data register address
            IN    AL,DX          ;Read high byte of A/D
            XCH   AH,AL          ;Store it in AH register

; Store result
            MOV   ES:[DI],AL     ;Store the low byte
            INC   DI
            MOV   ES:[DI],AH     ;Store the high byte
            INC   DI
            INC   CHNNO

;.....

; Next channel
;-----------
; Switch multiplexer
            MOV   DX,PORTA       ;Get port A address
            IN    AL,DX          ;Read port A
            AND   AL,11110000B   ;Set 4 LSBs to zero
            OR    AL,CHNNO       ;Set the channel number
            OUT   DX,AL          ;Write the bit pattern

;.....

; Provide delay for the window detector to settle
            MOV   BL,3
DELAY3:     DEC   BL
            JNZ   DELAY3

;.....

; Read window detector
            MOV   DX,PORTB       ;Get port B address
            IN    AL,DX          ;Read port B
```

```
                AND  AL,00000111B       ;Mask unwanted bits

;.....................................................
;
; Determine and store the gain code
                MOV  BL,0
                SHR  AL,1
                JNC  ADD3
                INC  BL
ADD3:           SHR  AL,1
                ADC  AL,BL
                MOV  ES:[DI],AL         ;Store the gain code
                MOV  AH,AL
                INC  DI                 ;Update byte counter

;.....................................................

; Set DT2805 board A/D parameters
; A/D mode
                MOV  DX,STCDRG          ;Get status register addr.
WAITA3:         IN   AL,DX              ;Repeat : read status reg.
                AND  AL,RDYBIT          ; Check the ready bit
                JZ   WAITA3             ;Until it is high
                MOV  AL,ADMODE          ;Get command mode
                OUT  DX,AL              ;Output it to command reg.

; Gain code
WAITG3:         IN   AL,DX              ;Repeat : read status reg.
                AND  AL,DINFULL         ; Check data in full bit
                JNZ  WAITG3             ;Until it is low
                MOV  DX,DATARG          ;Get data register addr.
                MOV  AL,AH              ;Get the gain code
                OUT  DX,AL              ;Write it to data register

; Channel number
                MOV  DX,STCDRG          ;Get status register addr.
WAITC3:         IN   AL,DX              ;Repeat : read status reg.
                AND  AL,DINFULL         ; Check data in full bit
                JNZ  WAITC3             ;Until it is low
                MOV  DX,DATARG          ;Get data register addr.
                MOV  AL,CHANNEL         ;Get channel number
                OUT  DX,AL              ;Write it into data reg.

;.....................................................

; Read and store A/D output
; Low byte
                MOV  DX,STCDRG          ;Get status register addr.
WAITL3:         IN   AL,DX              ;Repeat : read status reg.
                AND  AL,DOUTRDY         ; Check data out ready bit
                JZ   WAITL3             ;Until it is high
                MOV  DX,DATARG          ;Get data register addr.
                IN   AL,DX              ;Read low byte of A/D
                MOV  AH,AL              ;Store the value in AH reg.

; High byte
                MOV  DX,STCDRG          ;Get status register addr.
```

```
WAITH3:     IN    AL,DX          ;Repeat : read status reg.
            AND   AL,DOUTRDY     ; Check data out ready bit
            JZ    WAITH3         ;Until it is high
            MOV   DX,DATARG      ;Get data register addr.
            IN    AL,DX          ;Read high byte of A/D
            XCHG  AH,AL          ;Store high byte in AH reg.

; Store result
            MOV   ES:[DI],AL     ;Store the low byte
            INC   DI
            MOV   ES:[DI],AH     ;Store the high byte
            INC   DI
            INC   CHNNO

;.....

; Next channel
;-----------
; Switch multiplexer to next channel
            MOV   DX,PORTA       ;Get port A address
            IN    AL,DX          ;Read port A
            AND   AL,11110000B   ;Mask 4 LSBs
            OR    AL,CHNNO       ;Set the channel number
            OUT   DX,AL          ;Write the bit pattern

;.....

; Provide delay for the window detector to settle
            MOV   BL,3
DELAY4:     DEC   BL
            JNZ   DELAY4

;.....

; Read window detector output
            MOV   DX,PORTB       ;Get port B address
            IN    AL,DX          ;Read port B
            AND   AL,00000111B   ;Mask out unwanted bits

;.....

; Determine the store the gain code
            MOV   BL,0
            SHR   AL,1
            JNC   ADD4
            INC   BL
ADD4:       SHR   AL,1
            ADC   AL,BL
            MOV   ES:[DI],AL     ;Store the gain code
            MOV   AH,AL
            INC   DI             ;Update byte counter

;.....

; Set DT2805 A/D board parameters
; A/D mode
            MOV   DX,STCDRG      ;Get status register addr.
```

```
WAITA4:     IN    AL,DX          ;Repeat : read status reg.
            AND   AL,RDYBIT      ; Check the ready bit
            JZ    WAITA4         ;Until ready bit is high
            MOV   AL,ADMODE      ;Get command mode
            OUT   DX,AL          ;Output it to command reg.

; Gain code
WAITG4:     IN    AL,DX          ;Repeat : read status reg.
            AND   AL,DINFULL     ; Check data in full bit
            JNZ   WAITG4         ;Until it is low
            MOV   DX,DATARG      ;Get data register addr.
            MOV   AL,AH          ;Get the gain code
            OUT   DX,AL          ;Write it to data register

; Channel number
            MOV   DX,STCDRG      ;Get status register addr.
WAITC4:     IN    AL,DX          ;Repeat : read status reg.
            AND   AL,DINFULL     ; Check data in full bit
            JNZ   WAITC4         ;Until it is low
            MOV   DX,DATARG      ;Get data register addr.
            MOV   AL,CHANNEL     ;Get channel number
            OUT   DX,AL          ;Write it into data reg.

;.....

; Read & store A/D output
; Low byte
            MOV   DX,STCDRG      ;Get status register addr.
WAITL4:     IN    AL,DX          ;Repeat : read status reg.
            AND   AL,DOUTRDY     ; Check data out ready bit
            JZ    WAITL4         ;Until it is high
            MOV   DX,DATARG      ;Get data register address
            IN    AL,DX          ;Read low byte of A/D
            MOV   AH,AL          ;Store it in AH register

; High byte
            MOV   DX,STCDRG      ;Get status register addr.
WAITH4:     IN    AL,DX          ;Repeat : read status reg.
            AND   AL,DOUTRDY     ; Check data out ready bit
            JZ    WAITH4         ;Until it is high
            MOV   DX,DATARG      ;Get data register addr.
            IN    AL,DX          ;Read high byte of A/D
            XCHG  AH,AL          ;Store it in AH register

; Store A/D output
            MOV   ES:[DI],AL     ;Store the low byte
            INC   DI
            MOV   ES:[DI],AH     ;Store the high byte
            INC   DI
            INC   CHNNO

;.....

            CMP   CHNNO,MAXCHN   ;If channel no < 8 then
            JE    ENDINT         ;Read next channel
            JMP   NEXTCH
```

```
ENDINT:     MOV  DIREG,DI
            POP  DX                 ;Restore registers
            POP  BX
            POP  AX
            IRET                    ;Return from interrupt

ISRSAM      ENDP

;=================================================

; Initialise 8255A-5 PPI & disable interrupts
; Initialise PPI for ports A:O/P, B:I/P and C:O/P-I/P
ENDISR:     MOV  AX,CS
            MOV  DS,AX
            MOV  DX,CONREG          ;Get PPI cont. reg. addr.
            MOV  AL,82H             ;Get control reg. value
            OUT  DX,AL              ;Output bit pattern

; Disable interrupts
            CLI                     ;Disable interrupt
            MOV  DX,PORTA
            IN   AL,DX              ;Set sampling enable high
            JMP  $+2
            OR   AL,00010000B
            OUT  DX,AL
            JMP  $+2

;=================================================

; Store the ISR address at the interrupt vectors
            PUSH DS                 ;Save DS reg.
            MOV  AX,00              ;Set DS to zero
            MOV  DS,AX

; Sampling ISR vectors
; (For sampling ISR, hardware interrupt IRQ5 is used)
            MOV  BX,36H             ;CS of ISR at vector 36H
            MOV  WORD PTR [BX],CS
            MOV  BX,34H             ;Offset at vector 34H
            MOV  DX,STARTAD
            ADD  DX,OFFSET ISRSAM
            MOV  WORD PTR [BX],DX


            POP  DS                 ;Restore DS
            STI

;=================================================

; Initialise the interrupt controller #1
            MOV  AL,11H             ;ICW1, edge trigger, -
; Master with icw4
            OUT  INTA00,AL
```

```
                JMP   $+2               ;Wait state for i/o
                MOV   AL,8              ;ICW2, interrupt type 2
                OUT   INTA01,AL

                JMP   $+2               ;Wait state for i/o
                MOV   AL,4              ;ICW3, -
; Master controller level 2
                OUT   INTA01,AL

                JMP   $+2               ;Wait state for i/o
                MOV   AL,1              ;ICW4, master, 80286 mode
                OUT   INTA01,AL

                JMP   $+2               ;Wait state for i/o
                IN    AL,INTA01         ;Get interrupt
; Mask register imr contents
                AND   AL,11011111B      ;Enable interrupt level 5
                OUT   INTA01,AL         ;Put new bit pattern in imr.

;=================================================

;Initialise the program variables
                MOV   SI,RESPTME        ;SI reg. = 1st RT location
                MOV   RESPTR,SI
                MOV   DI,ADOFFST        ;DI reg. = 1st CNV ampl.
                MOV   DIREG,DI

                MOV   SAMPNO,0          ;Initialise sample number
                MOV   CHNNO,0           ;Initialise channel number
                MOV   AX,ADSEG          ;Initialise es register
                MOV   ES,AX

                MOV   AX,[BP+4]         ;Get trial number
                MOV   TRIAL,AX          ;Record trial number
                MOV   TRIALST,AX

; Determine sample number
                MOV   AX,[BP+6]         ;Get post-imp.-sti. time
                MOV   BX,SAMPRT         ;Sampling freq = 125
                MUL   BX                ;AX:= AX * BX
                MOV   POSTCNV,AX        ;Post-imp.-sti. sam. no.

                MOV   AX,[BP+8]         ;Get ISI time
                MOV   BX,SAMPRT
                MUL   BX                ;ISI sample no.
                MOV   CNV,AX

                MOV   AX,[BP+10]        ;Get pre-war.-sti. time
                MOV   BX,SAMPRT
                MUL   BX                ;Pre-war.-sti. sam. no.
                MOV   PRECNV,AX

                MOV   AX,PRECNV         ;Adjust pre-war.-sti.
                ADD   AX,CNV
                MOV   CNV,AX
```

```
                MOV  AX,CNV             ;Adjust post-imp.-sti.
                ADD  AX,POSTCNV
                MOV  POSTCNV,AX

;=======================================

; Determine total number of bytes / trial
                MOV  AX,POSTCNV         ;Add to post-imp. sam. no.
                MOV  BX,24
; (8-channel * 3 bytes / sample = 24)
                MUL  BX
; (Total bytes / trial = total sample * 24)
                MOV  BYTESUM,AX         ;Store the result

;=======================================

; Create CNV file on hard disk
                MOV    AX,CS            ;Initialise ds reg.
                MOV    DS,AX

                MOV  DX,STARTAD         ;Get proc. start addr.
                ADD  DX,OFFSET CNVFILE ;Initialise dx reg.
                MOV  AH,CREFILE         ;Ah reg. = create code
                MOV  CX,FILEATR         ;Cx reg. = file attribute
                INT  21H                ;Call dos function

;=======================================

; Open the CNV file created
                MOV  DX,STARTAD         ;Get proc. starting addr.
                ADD  DX,OFFSET NETPATH ;Initialise dx reg.

                MOV  AH,OPENFIL         ;Get open file code
                MOV  AL,ACCODE          ;Al reg. = access code
                INT  21H                ;Call dos function
                MOV  FILEHDL,AX         ;Store file handle

;=======================================

; Initialise counters  #0 and #2
; Counter #0
; (This counter is used to divide the 1.5MHz clock signal
; by 1500)

                MOV  AL,00110110B       ;Set counter 0 cont. reg.
                MOV  DX,CONTREG         ;Get control reg. address
                OUT  DX,AL              ;Write bit pattern

                MOV  AL,11011100B       ;Set counter 0 to 1500
; (1500 = 05DCH)
                MOV  DX,COUNTR0         ;Get counter 0 address
                OUT  DX,AL              ;Write the low byte
```

```
                JMP   $+2
                MOV   AL,00000101B
                OUT   DX,AL             ;Write the high byte

; COUNTER #2
; (This counter is initialised to provide the sampling
;  signal, initial counter value 12000, 2EE0H)

                MOV   AL,10110110B      ;Set counter2 control reg.
                MOV   DX,CONTREG        ;Get control reg. address
                OUT   DX,AL             ;Write bit pattern
                MOV   AL,11100000B      ;Write counter LSB
                MOV   DX,COUNTR2
                OUT   DX,AL
                JMP   $+2
                MOV   AL,00101110B      ;Write counter MSB
                OUT   DX,AL

;=================================================

; Push_button error detection initialisation routine
REPEAT:         MOV   DX,PORTC          ;Get port C address
                IN    AL,DX             ;Read port C
                JMP   $+2
                AND   AL,11111101B
; Set error detector circuit output low
                OUT   DX,AL
                JMP   $+2
                JMP   $+2
                JMP   $+2
                JMP   $+2
                MOV   DX,PORTC
; Enable the error detector circuit
                IN    AL,DX
                OR    AL,00000010B
                OUT   DX,AL
                JMP   $+2
                MOV   FLAG,0            ;Clear error det. flag

;=================================================

; Generate a random number.
; The number is produced by reading the two l.s.b.s of the
; system clock then adding one to it and multiplying the
; result by 100, providing 100 to 400.
                MOV   AH,00             ;Prepare ah register
                INT   1AH               ;Call bios to read clock
; Low byte of the clock output is in dx register
                MOV   AX,DX
                AND   AL,00000011B      ;Mask out unwanted bits
                ADD   AL,1              ;Add one to the result
                MOV   AH,00             ;Reset AH reg.
                MOV   BX,100
```

```
                MUL  BX                 ;AX := AX * BX
                MOV  RANDNO,AX          ;Save the number generated

;=======================================

; Initialise 8253, PTM #2 counter #0.
; This counter is used for reaction time measurement
; Its gate is connected to tone generator circuit.
                MOV  AL,00110000B       ;CTR0, mode 0, 16-bit
                MOV  DX,PTM2CRG         ;Get control reg. address
                 OUT  DX,AL             ;Write the bit pattern

; Counter initial value = FFFFH
                MOV  AL,0FFH
                MOV  DX,PTM2CR0
                OUT  DX,AL
                JMP  $+2
                OUT  DX,AL

;=======================================

; Switch the operator LED off
; (This LED is connected to port A bit 5)
                MOV  DX,PORTA           ;Get port A address
                IN   AL,DX              ;Read port A
                AND  AL,11011111B       ;Set bit 5 low
                JMP  $+2
                OUT  DX,AL

;=======================================

; Check the operator switch for initiation of trials
; (Operator switch is connected to port B bit 4)
                MOV  DX,PORTB           ;Get port B address
NOTRDY:         IN   AL,DX              ;Repeat : read port B
                JMP  $+2
                AND  AL,00010000B       ; Check bit 4
                JZ   NOTRDY             ;Until ready condition

;=======================================

; Switch the LED on to indicate recording started
                MOV  DX,PORTA           ;Get port A address
                IN   AL,DX              ;Read port A
                OR   AL,00100000B       ;Set bit 5 high
                JMP  $+2
                OUT  DX,AL

;=======================================

; Enable sampling interrupt
```

```
                STI                     ;Enable processor interrupt
                MOV  DX,PORTA           ;Enable sampling interrupt
                IN   AL,DX
                AND  AL,11101111B
                OUT  DX,AL
                JMP  $+2

;=======================================

; Wait until pre-warning-stimulus recording is complete
                MOV  AX,CS
                MOV  DS,AX
PRECS:          STI
                MOV  AX,PRECNV
                CMP  AX,SAMPNO
                JNE  PRECS

;=======================================

; Trigger click generator
                MOV  DX,PORTA           ;Get port a address
                IN   AL,DX              ;Read port A
                OR   AL,01000000B       ;Set bit 6 high
                OUT  DX,AL

                MOV  BL,3               ;Provide delay
HCLICK:         DEC  BL
                JNZ  HCLICK

                AND  AL,10111111B       ;Set bit 6 low
                OUT  DX,AL

                MOV  BL,3               ;Provide delay
LCLICK:         DEC  BL
                JNZ  LCLICK

                OR   AL,01000000B       ;Set bit 6 high again
                OUT  DX,AL

;=======================================

; Wait until inter-stimulus-interval recording is complete
CNVS            STI
                MOV  AX,CNV
                CMP  AX,SAMPNO
                JNE  CNVS

;=======================================

; Check if error has occurred in pressing push-button
                MOV  DX,PORTB           ;Get portB address
                IN   AL,DX              ;Read portB
                JMP  $+2
```

```
; Check the output of the error detector circuit
                AND   AL,00100000B
                JZ    TONE              ;If no error then tone
                MOV   FLAG,1            ;Else set error flag to 1
                JMP   SHORT PCNVS       ;No tone if error

;=================================================

; Generate the tone (if no error in pressing push-button)
TONE:           MOV   DX,PORTA          ;Get port A address
                IN    AL,DX             ;Read port A
                OR    AL,10000000B      ;Set tone line high
                OUT   DX,AL

                MOV   BL,3
HTONE:          DEC   BL
                JNZ   HTONE

                JMP   $+2
                AND   AL,01111111B      ;Set tone line low
                OUT   DX,AL
                JMP   $+2

                MOV   BL,3              ;Provide delay
LTONE:          DEC   BL
                JNZ   LTONE
                JMP   $+2

                OR    AL,10000000B      ;Set tone line high again
                OUT   DX,AL

;=================================================

; Wait for post-imperative-stimulus recording
PCNVS           STI
                MOV   AX,POSTCNV
                CMP   AX,SAMPNO
                JNE   PCNVS

;=================================================

; Disable sampling
                CLI
                MOV   DX,PORTA          ;Get port A
                IN    AL,DX
                JMP   $+2
                OR    AL,00010000B      ;Set sampling line(4) high
                OUT   DX,AL
                JMP   $+2

;=================================================

; Read and store reaction time (RT) from PTM2 counter #0
```

```
                MOV  AL,00000000B       ;Control reg. read mode
                MOV  DX,PTM2CRG
                OUT  DX,AL
                MOV  DX,PTM2CR0
                IN   AL,DX              ;Read lower byte
                JMP  $+2
                MOV  AH,AL
                IN   AL,DX              ;Read most sig. byte
                XCHG AL,AH

                MOV   CX,AX             ;RT := FFFFHex - AX
                MOV   AX,1111111111111111B
                SUB   AX,CX

                CMP  FLAG,0             ;Check if error occurred
                JE   STRESP
                JMP  SHORT INITPS       ;If flag = 1 then error

; Store the reaction time
STRESP:         MOV  SI,RESPTR
                MOV  ES:[SI],AX         ;Store reaction time
                ADD  SI,2
                MOV  RESPTR,SI

;=======================================

; Initiate the ISI random time
; ISI timing is done by PTM1 counter #1
INITPS:         MOV  DX,PORTC           ;Get port C address
                IN   AL,DX              ;Read port C
                AND  AL,11111110B       ;Disable the counter
                OUT  DX,AL

; Control register: mode 0, 16-bits
                MOV  AL,01110000B
                MOV  DX,CONTREG
                OUT  DX,AL

                MOV  AX,RANDNO          ;Get random number
                MOV  DX,COUNTR1         ;Get counter1 address
                OUT  DX,AL              ;Write the low byte
                JMP  $+2
                MOV  AL,AH
                OUT  DX,AL              ;Write the high byte

; Enable counter #1
                MOV  DX,PORTC           ;Get port C address
                IN   AL,DX
                OR   AL,00000001B       ;Set counter gate high
                OUT  DX,AL

;=======================================

; Wait until ISI is over by looking at port B bit 3
                MOV  DX,PORTB           ;Read port B
```

```
PAUSE:      IN    AL,DX
            AND   AL,00001000B      ;If Bit = 0 then
            JZ    PAUSE             ;Wait

;=========================================

; Write A/D output to hard disk
WRITE:      CMP   FLAG,1            ;Check for trial error
            JE    CHECK             ;If error then skip data
            MOV   BX,FILEHDL        ;Get file handle into BX
            MOV   DX,ADOFFST        ;DX = offset address
            MOV   CX,BYTESUM        ;CX = no. of bytes/trial
            MOV   DI,ADSEG          ;DS = segment address

            MOV   DS,DI
            MOV   H,WRCODE          ;Get write code
; (N.B. the AH reg. value is changed after int. 21h)

            STI
            INT   21H               ;Call dos function

            MOV   AX,CS             ;Reinitialise ds reg.
            MOV   DS,AX

;=========================================

; Check the number of trials recorded
CHECK       CMP   FLAG,1            ;Check for error
; If error has occurred, do not decrease trial no.
            JE    NOTDEC

            DEC   TRIAL             ;Update trial no.
NOTDEC:     MOV   SAMPNO,0          ;Update sample number
            MOV   DI,ADOFFST        ;Update the byte pointers
            MOV   DIREG,DI
            MOV   AX,TRIAL          ;Get no. of trials recorded
            CMP   AX,0              ;If trial = 0 then
            JE    RESPT             ;Experiment complete
            JMP   REPEAT            ;Else do next trial

;=========================================

; Routine to store the reaction times on the hard disk
RESPT:      MOV   AX,TRIALST        ;Determine the no. of -
            MOV   BX,2              ; reaction time bytes
            MUL   BX
            MOV   CX,AX             ;Store byte no. into CX
            MOV   BX,FILEHDL        ;Get the file handle
            MOV   DX,RESPTME        ;Get RTs 1st location
            MOV   DI,ADSEG          ;Get segment address
            MOV   DS,DI
            MOV   AH,WRCODE         ;Get the write code
            INT   21H               ;Transfer the data
```

```
                MOV  AX,CS
                MOV  DS,AX

;=================================================

; Close the CNVAMP.DAT file
EXIT:           MOV  BX,FILEHDL      ;Get the file handle
                MOV  AH,CLOSFIL      ;Get code for closing file
                INT  21H             ;Call dos function
                JMP  POPREG

;=================================================

; Restore the registers
POPREG:         POP  SI
                POP  DI
                POP  DS
                POP  DX
                POP  CX
                POP  BX
                POP  AX
                MOV  SP,BP
                POP  BP

;=================================================

; Deallocate variable from stack and return to Pascal prog.
                RET  8

SAMPLE  ENDP                         ;End sample procedure

CODE            ENDS                 ;End code segment
                END   SAMPLE         ;End routine

;**************** END OF SAMPLE1 PROCEDURE ***********
```

Appendix B List of Patients' Medication

The type of medication for the schizophrenic patients included chlorpromazine (n=5), trifluoperazine (n=4), haloperidol (n=3), clopenthixol (n=2), droperidol (n=1), sulpiride (n=4), pimozoide (n=1), fluphenazine decanoate (n=5) and haloperidol decanoate (n=2). The daily dosage of these drugs in chlorpromazine equivalents ranged from 100mg to 3025mg, mean was 1178mg and standard deviation was 933.32mg. The type of medication for the Parkinson's disease patients included sinemet, madopar, bromocriptine, domperidone and selegiline. The type of medication for the Huntington's disease patients included motipress and kurispas.

Appendix C Listing of the Program Used to Preprocess and Average the CNV Waveforms and to Convert the Data Recordings for Transfer to the Mainframe Computer

```
PROGRAM PROC;

{ Program name = PROC.PAS
  This Turbo Pascal program can preprocess and average the CNV
  waveforms using a PC or if is required it can prepare the data
  to be preprocessed on the IBM main frame computer.
}

CONST
        XP = 5;
        YP = 5;

TYPE
        DATA_ARRAY = ARRAY [1..1500] OF INTEGER;
        MATRIX     = ARRAY [1..4, 1..4] OF REAL;
        VECTOR     = ARRAY [1..4] OF REAL;
        REAL_ARRAY = ARRAY [1..100] OF REAL;
        REAL_DATA  = ARRAY [1..1500] OF REAL;

VAR
        OPTION : CHAR;
        HN_FIL : TEXT;
        VL_RE, VR_RE, HL_RE, HR_RE : REAL_DATA;
        CNV_RE, CNV, AVERAGE_CNV   : REAL_DATA;

{-------------------------------------------------}


PROCEDURE MATRIX_SOL (A : MATRIX;
                      B : VECTOR;
                      VAR X : VECTOR;
                      VAR SINGULARITY_DETECTED :
BOOLEAN);

CONST
        N = 4;

TYPE
        SUBSCRIPT = 1..N;


PROCEDURE ELIMINATION       (N : INTEGER;
                             VAR A : MATRIX;
                             VAR B : VECTOR);

CONST
        ASSUMED_ZERO = 0.00001;

VAR
        I,J, K : SUBSCRIPT;
        MULTIPLIER : REAL;
```

```
PROCEDURE SWAP (VAR X,Y : REAL);

VAR
        T : REAL;

BEGIN
        T := X;
        X := Y;
        Y := T
END;

PROCEDURE REORDEREQUATIONS      (N, I : INTEGER;
                                 VAR A : MATRIX;
                                 VAR B : VECTOR);

VAR
        K, L, J : SUBSCRIPT;

BEGIN
        L := I;
        FOR K := I+1 TO N DO
        IF ABS(A[K,I]) > ABS(A[L,I]) THEN
         L := K;

        IF ABS (A[L,I]) <= ASSUMED_ZERO THEN
        SINGULARITY_DETECTED := TRUE
        ELSE
                IF I <> L THEN
                BEGIN
                        FOR J := I TO N DO
                        SWAP (A[I,J], A[L,J]);
                        SWAP(B[I], B[L])
                END
END; {reorderequations}


BEGIN {eliminations}
        SINGULARITY_DETECTED := FALSE;
        I := 1;
        REPEAT
                REORDEREQUATIONS (N,I,A,B);
                IF NOT SINGULARITY_DETECTED THEN
                FOR K := I+1 TO N DO
                BEGIN
                        MULTIPLIER := A[K,I] / A[I,I];
                        FOR J:= I+1 TO N DO
                        A[K,J] := A[K,J] - MULTIPLIER * A[I,J];
                        B[K] := B[K] - MULTIPLIER * B[I];
                        A[K,I] := 0;
                        END;
                        I := I + 1;
        UNTIL (I = N) OR SINGULARITY_DETECTED;
        IF NOT SINGULARITY_DETECTED THEN
        SINGULARITY_DETECTED := ABS(A[N,N]) <= ASSUMED_ZERO
```

```
END; {elimination}


PROCEDURE BACK_SUBST (N : INTEGER;
                      VAR A : MATRIX;
                      VAR B,X : VECTOR);

VAR
        I, J : SUBSCRIPT;
        S : REAL;

BEGIN
        FOR I := N DOWNTO 1 DO
        BEGIN
                S := B[I];
                FOR J := I + 1 TO N DO
                S := S - A[I,J] * X[J];
                X[I] := S / A[I,I]
        END
END;



BEGIN
        {main procedure}

        ELIMINATION (N,A,B);
        IF SINGULARITY_DETECTED THEN
        BEGIN
                WRITELN;
                WRITELN ('The equations are singular.');
                WRITELN ('Corrective action taken.')
        END {begin}

        ELSE
                BACK_SUBST (N,A,B,X);
END;

{-------------------------------------------------}

PROCEDURE MEAN  (SAMPLES : INTEGER;
                 VAR DATA : DATA_ARRAY);

{Procedure to remove the mean from data}

VAR
        I : INTEGER;
        MEAN_VALUE : REAL;

BEGIN
        MEAN_VALUE := 0;
        FOR I :=1 TO SAMPLES DO
        MEAN_VALUE := MEAN_VALUE + DATA [I];
        MEAN_VALUE := MEAN_VALUE / SAMPLES;
        FOR I := 1 TO SAMPLES DO
        DATA[I] := ROUND(DATA[I] - MEAN_VALUE);
END;
```

```
{-------------------------------------------------}

PROCEDURE OARM  (SAMPLES : INTEGER;
                 VAR VL, VR, HL, HR : DATA_ARRAY;
                 RAD, NEW_MONT : CHAR;
                 VAR CNV : DATA_ARRAY;
                 VAR SINGULARITY_DETECTED : BOOLEAN);

{Procedure to correct CNV data by removing OA}


VAR
        I : INTEGER;
        PVL, B, CCL, C, PVR, D, CCR, PHL : REAL;
        MVL, MVR, MHL, MHR, A, PHR : REAL;
        X : MATRIX;
        Y, K : VECTOR;

BEGIN

        {convert signals from uV to mV}
        FOR I := 1 TO SAMPLES DO
        BEGIN
                VL_RE[I] := VL[I] * 0.001;
                VR_RE[I] := VR[I] * 0.001;
                HL_RE[I] := HL[I] * 0.001;
                HR_RE[I] := HR[I] * 0.001;
                CNV_RE[I] := CNV[I] * 0.001
        END;


        IF ((NEW_MONT='Y')OR(NEW_MONT='y')) AND
        ((RAD<>'R')AND(RAD<>'r')) THEN
        {new montage, without rad. components}
        BEGIN
                FOR I := 1 TO SAMPLES DO
                VL_RE[I] := HL_RE[I] * HR_RE[I]
        END
        ELSE
        IF (RAD <>'R') AND (RAD <>'r') THEN
        {old montage}
        BEGIN
                {calculate VL components}
                FOR I := 1 TO SAMPLES DO
                VL_RE[I] := HL_RE[I] * HR_RE[I]
        END;

        {calculate correlation sum of product}
        PVL := 0;
        B   := 0;
        CCL := 0;
        C   := 0;
        PVR := 0;
        D   := 0;
        CCR := 0;
```

```
PHL := 0;
A   := 0;
PHR := 0;
MVL := 0;
MVR := 0;
MHL := 0;
MHR := 0;

FOR I :=1 TO SAMPLES DO
BEGIN
        PVL := PVL + VL_RE[I] * VL_RE[I];
        B   := B   + VL_RE[I] * VR_RE[I];
        CCL := CCL + VL_RE[I] * HL_RE[I];
        C   := C   + VL_RE[I] * HR_RE[I];
        PVR := PVR + VR_RE[I] * VR_RE[I];
        D   := D   + VR_RE[I] * HL_RE[I];
        CCR := CCR + VR_RE[I] * HR_RE[I];
        PHL := PHL + HL_RE[I] * HL_RE[I];
        A   := A   + HL_RE[I] * HR_RE[I];
        PHR := PHR + HR_RE[I] * HR_RE[I]
END;

FOR I := 1 TO SAMPLES DO
BEGIN
                MVL := MVL + CNV_RE[I] * VL_RE[I];
                MVR := MVR + CNV_RE[I] * VR_RE[I];
                MHL := MHL + CNV_RE[I] * HL_RE[I];
                MHR := MHR + CNV_RE[I] * HR_RE[I]
END;

{find K1, K2, K3 and K4}

X[1,1] := PVL;
X[1,2] := B;
X[1,3] := CCL;
X[1,4] := C;
X[2,1] := B;
X[2,2] := PVR;
X[2,3] := D;
X[2,4] := CCR;
X[3,1] := CCL;
X[3,2] := D;
X[3,3] := PHL;
X[3,4] := A;
X[4,1] := C;
X[4,2] := CCR;
X[4,3] := A;
X[4,4] := PHR;

Y[1] := MVL;
Y[2] := MVR;
Y[3] := MHL;
Y[4] := MHR;

MATRIX_SOL (X, Y, K, SINGULARITY_DETECTED);

IF NOT SINGULARITY_DETECTED THEN
```

```
        BEGIN
                {correct the CNV channel}
                FOR I := 1 TO SAMPLES DO
                CNV_RE[I] := CNV_RE[I] -
                (K[1] * VL_RE[I] + K[2] * VR_RE[I] +
                        K[3] * HL_RE[I] + K[4] * HR_RE[I]);

        {convert CNV signal back to uV}
        FOR I := 1 TO SAMPLES DO
                CNV[I] := ROUND (CNV_RE[I] * 1000);
        END;{BEGIN}

END; {OAR procedure}

{-------------------------------------------------}


PROCEDURE SECTAV        (NPA, NPB : INTEGER;
                         CNV      : REAL_DATA;
                         VAR SAV  : REAL);

{procedure to average the points between NPA & NPB
 of the CNV data}

VAR
        I : INTEGER;

BEGIN
        SAV := 0;
        FOR I := NPA TO NPB DO
        SAV := SAV + CNV[I];
        SAV := SAV / (NPB - NPA);

        END; {procedure sectav}

{-------------------------------------------------}


PROCEDURE BAS_LNE       (N, NP1, NP2, NP3, NP4 : INTEGER;
                         VAR CNV : REAL_DATA);

{procedure to correct the baseline of the CNV signal}

VAR
        I, Z1, Z2 : INTEGER;
        SAV1, SAV2, GRAD : REAL;

BEGIN
        SECTAV (NP1, NP2, CNV, SAV1);
        SECTAV (NP3, NP4, CNV, SAV2);
        GRAD := (SAV2 - SAV1) / (NP3 - NP2);

        FOR I := 1 TO NP2 DO
        CNV[I] := CNV[I] - SAV1;

        Z1 := NP2 + 1;
        FOR I := Z1 TO NP3 DO
```

```
        CNV[I] := CNV[I] - SAV1 - GRAD * (I - NP2);

        Z2 := NP3 + 1;
        FOR I := Z2 TO N DO
        CNV[I] := CNV[I] - SAV2;

END; {procedure bas_lne}

{-------------------------------------------------}


PROCEDURE FILTER (SAMPLES, M : INTEGER;
                  H        : REAL_ARRAY;
                  VAR CNV  : REAL_DATA);

{procedure to low-pass filter the CNV data using FIR.
 The number of data points is equal to samples and
 the data is returned is CNV array}

VAR
        K, NEW, N, FILT_SAMP : INTEGER;
        SUM                  : REAL;
        YOUT                 : REAL_DATA;
        X                    : ARRAY [1..100] OF REAL;


BEGIN
        {initialise the filter buffer}
        FOR K := M DOWNTO 1 DO
        BEGIN
                N := 1;
                X[K] := CNV[N];
                N := N + 1;
        END;

        NEW := M;
        FILT_SAMP := SAMPLES - M;

        {do the filtering}
        FOR N := 1 TO FILT_SAMP DO
        BEGIN
                SUM := 0;
                FOR K := 1 TO M DO
                        SUM := SUM + H[K] * X[K];
                YOUT[N] := SUM;

                {shift new data into x[n] buffer}
                FOR K := M DOWNTO 2 DO
                        X[K] := X[K-1];
                NEW := NEW + 1;
                X[1] := CNV[NEW];
        END;{for}

        FILT_SAMP := FILT_SAMP + 1;
        SUM := 0;
        FOR K := 1 TO M DO
        SUM := SUM + H[K] * X[K];
```

```
        YOUT [FILT_SAMP] := SUM;

        FILT_SAMP := FILT_SAMP + 1;
        FOR N := FILT_SAMP TO SAMPLES DO
        YOUT[N] := 0;

        FOR K := 1 TO SAMPLES DO
        CNV[K] := YOUT[K]

END; {procedure filter}

{-------------------------------------------------}


PROCEDURE CONVERT;

{procedure to convert a data file to the format
 required for preprocessing on the mainframe
 computer or preprocess the data on a PC}

CONST
        SAMPLE_RATE = 125;
        CHANNEL_NO  = 8;
        RANGE       = 20;
        BASE_FACTOR = 4096;
        MAX_VOLTAGE = 10;

        {baseline correction points}
        NP1 = 1;   {initial point}
        NP2 = 125;  {S1 point}
        NP3 = 250;  {S2 point}
        NP4 = 1500; {final point}

TYPE
        NAME = STRING [12];

VAR
        NO1, NO2, NUMBER, AD_GAIN, TRIAL : INTEGER;
        CHANNEL, BI_VOLT, N, M, I, SAMPLES : INTEGER;
        MAX_BATCH, BATCH_NO, DURATION, TRIAL_NO : INTEGER;
        PCH1, PCH2, PCH3, PCH4, PCH5 : INTEGER;
        FACTOR, RESOLUTION, TIME : REAL;
        VL, VR, VRC, VRR, HL, HR, CNV1, CNV2 : DATA_ARRAY;
        H : REAL_ARRAY;
        ORG_FILE_NAME, CONV_FILE_NAME, SIN_TRI_NAM : NAME;
        ORG_FILE, CONV_FILE, SIN_TRI_FIL : TEXT;
        COMP_OUTPUT, ELEMENT1, ELEMENT2, A, RAD : CHAR;
        BASE_LINE, FILTERING, DECISION, OAR_INC : CHAR;
        NEW_MONT, OAR_OPTION, SIN_TRI_OP : CHAR;
        RE_ENTER : BOOLEAN;
        K : VECTOR;
        TRIAL_SET : SET OF 1..32;
        SINGULARITY_DETECTED : BOOLEAN;


BEGIN
        REPEAT
```

```
        CLRSCR;
        WRITELN ('****************************************');
        WRITELN ('* Routine to preprocess the CNV data *');
        WRITELN ('* on the PC or prepare the CNV data  *');
        WRITELN ('* for processing on the mainframe    *');
        WRITELN ('****************************************');
        RE_ENTER := FALSE;
        WRITELN;
        WRITELN;
        WRITELN ('Please enter the following :');
        WRITELN;

        WRITE ('The original data filename : ');
        READLN (ORG_FILE_NAME);
        WRITE ('The converted file name : ');
        READLN (CONV_FILE_NAME);
        WRITE ('Channel 1 to 5 polarities 1/-1 : ');
        READLN (PCH1, PCH2, PCH3, PCH4, PCH5);
        WRITE ('The number of trials in the recording : ');
        READLN (TRIAL);
        WRITE ('Include all trials ? Enter "Y" or "N" : ');
        READLN (DECISION);
        TRIAL_SET := [];
        IF (DECISION ='Y') OR (DECISION ='y') THEN
        BEGIN
                FOR N := 1 TO TRIAL DO
                TRIAL_SET := TRIAL_SET + [N];
        END
ELSE
        BEGIN
                WRITE ('How many trials to be included : ');
                READLN (TRIAL_NO);
                FOR I:=1 TO TRIAL_NO DO
                BEGIN
                        WRITE ('The required trial number : ');
                        READLN (NUMBER);
                        TRIAL_SET := TRIAL_SET + [NUMBER];
                END;{for}
        END;{else}

WRITE ('The duration of each trial : ');
READLN (DURATION);


WRITE ('Is recording done with new montage?');
WRITE (', Y or N : ');
READLN (NEW_MONT);
IF (NEW_MONT = 'N') OR (NEW_MONT ='n') THEN
RAD := 'N'
ELSE
BEGIN
        WRITE ('To include radial components in OAR');
        WRITE (' enter "R", else "N" : ');
        READLN (RAD);
END; {else}

WRITE ('PC preprocessing, enter "P",');
```

```
WRITE (' MF preprocessing enter "M" : ');
READLN (OAR_OPTION);

IF (OAR_OPTION = 'P') OR (OAR_OPTION = 'p') THEN
BEGIN
        WRITE ('For Baseline correction enter "B",');
        WRITE (' else "N" : ');
        READLN (BASE_LINE);
        WRITE ('Carry out OAR ?, "Y" or "N" : ');
        READLN (OAR_INC);
        WRITE ('For digital filtering, enter "F", ');
        WRITE ('else "N" : ');
        READLN (FILTERING);

        WRITE ('For single trial file ');
        WRITE ('enter "S", else "N" : ');
        READLN (SIN_TRI_OP);
        IF (SIN_TRI_OP = 'S')OR(SIN_TRI_OP = 's') THEN
        BEGIN
        WRITE ('Enter single trial filename : ');
         READLN (SIN_TRI_NAM);
        END; {if}
END; {if}

WRITELN;
WRITELN;
WRITE('Above entries OK ?  "Y", or "N" : ');
READLN (A);
IF (A='Y') OR (A='y') THEN
RE_ENTER := TRUE;
UNTIL RE_ENTER = TRUE;

CLRSCR;

ASSIGN (ORG_FILE, ORG_FILE_NAME);
RESET (ORG_FILE);
ASSIGN (CONV_FILE, CONV_FILE_NAME);
REWRITE (CONV_FILE);

IF (SIN_TRI_OP = 'S') OR (SIN_TRI_OP = 's') THEN
BEGIN
ASSIGN (SIN_TRI_FIL, SIN_TRI_NAM);
REWRITE (SIN_TRI_FIL);
END;{if}

IF (FILTERING = 'F') OR (FILTERING = 'f') THEN
{if filtering option then read the coefficients}
BEGIN
        ASSIGN (HN_FIL, 'HNVALS.DAT');
        RESET (HN_FIL);
        READLN (HN_FIL, M);
        FOR N := 1 TO M DO
        READLN (HN_FIL, H[N]);
        CLOSE (HN_FIL);
END;{for}
```

```
RESOLUTION := RANGE / BASE_FACTOR;
SAMPLES := SAMPLE_RATE * DURATION;

{initialise variables}
BATCH_NO := 0;
FOR I:=1 TO SAMPLES DO
        AVERAGE_CNV[I] := 0;

FOR N :=1 TO TRIAL DO
        BEGIN
        IF (N IN TRIAL_SET) THEN
        BEGIN

        GOTOXY(XP+13,YP+8);
        WRITE ('Processing trial number ',n:3);

        {read data for one trial}
        I :=1;
        REPEAT
                FOR CHANNEL := 1 TO 6 DO
                BEGIN
                        READ (ORG_FILE, COMP_OUTPUT,
                        ELEMENT1, ELEMENT2);
                        NO1 := ORD(ELEMENT1);
                NO2 := ORD(ELEMENT2);
                NUMBER := NO1 + (NO2 * 256);
                FACTOR := RESOLUTION * NUMBER;
                CASE ORD(COMP_OUTPUT) OF
                                0 : AD_GAIN := 1;
                                1 : AD_GAIN := 10;
                                2 : AD_GAIN := 100;
                                3 : AD_GAIN := 500;
                        END; {end}

                        BI_VOLT := ROUND (( (FACTOR -
                        MAX_VOLTAGE)/AD_GAIN ) * 200);
                        CASE CHANNEL OF
                                1 : VL [I] := PCH1 * BI_VOLT;
                                2 : VR [I] := PCH2 * BI_VOLT;
                                3 : HL [I] := PCH3 * BI_VOLT;
                                4 : HR [I] := PCH4 * BI_VOLT;
                                5 : CNV1 [I] := PCH5 * BI_VOLT;
                                6 : CNV2 [I] := PCH5 * BI_VOLT;
                END; {case}
        END; {for channel}

        READ (ORG_FILE, A,A,A,A,A,A);

        I := I + 1;
UNTIL I = SAMPLES + 1;


{process the data if radial components is included}
IF (RAD='R') OR (RAD='r') OR (NEW_MONT='Y')
OR (NEW_MONT='y') THEN
BEGIN
        FOR I:= 1 TO SAMPLES DO
```

```
                BEGIN
                        {calculate the radial right, VL
                        and VR components}
                        VRC[I] := VL[I] - VR[I]; {ver. right}
                        IF (RAD='R') OR (RAD='r') THEN
                        {radial right}
                        VRR[I] := ROUND (0.5 * (VL[I] + VR[I]))
                        ELSE
                                VRR[I] := 0;
                {vertical or radial right}
                VL[I]  := VRR[I];
                VR[I]  := VRC[I]; {vertical right}
                {reorder channel 3 and 4}
                VRR[I] := HL[I];
                HL[I] := HR[I];
                HR[I] := VRR[I];
                {when rad. comp. is included VRR refers to
                to rad. comp. and VRC refers to vert.
                right comp.}
        END; {for}
END; {if)


{if MF OAR is required, form a converted file}
IF (OAR_OPTION ='M') OR (OAR_OPTION ='m') THEN
BEGIN

                {write data for one trial into the
                converted file}
                WRITELN (CONV_FILE, BATCH_NO:4);
                FOR I := 1 TO 1024 DO
                BEGIN
                        WRITE (CONV_FILE, VL[I]:5);
                        IF I MOD 16 = 0 THEN
                        WRITELN (CONV_FILE);
                END;
                BATCH_NO := BATCH_NO +1;

                WRITELN (CONV_FILE, BATCH_NO:4);
                FOR I := 1 TO 1024 DO
                BEGIN
                        WRITE (CONV_FILE, VR[I]:5);
                        IF I MOD 16 = 0 THEN
                        WRITELN (CONV_FILE);
                END;
                BATCH_NO := BATCH_NO +1;

                WRITELN (CONV_FILE, BATCH_NO:4);
                FOR I := 1 TO 1024 DO
                BEGIN
                        WRITE (CONV_FILE, HL[I]:5);
                        IF I MOD 16 = 0 THEN
                        WRITELN (CONV_FILE);
                END;
                BATCH_NO := BATCH_NO +1;

                WRITELN (CONV_FILE, BATCH_NO:4);
```

```
                FOR I:= 1 TO 1024 DO
                BEGIN
                        WRITE (CONV_FILE, HR[I]:5);
                        IF I MOD 16 = 0 THEN
                        WRITELN (CONV_FILE);
        END;
        BATCH_NO := BATCH_NO +1;

        WRITELN (CONV_FILE, BATCH_NO:4);
        FOR I:= 1 TO 1024 DO
        BEGIN
                WRITE (CONV_FILE, CNV1[I]:5);
                IF I MOD 16 = 0 THEN
                WRITELN (CONV_FILE);
                END;
                BATCH_NO := BATCH_NO +1;

                WRITELN (CONV_FILE, BATCH_NO:4);
                FOR I := 1 TO 1024 DO
                BEGIN
                        WRITE (CONV_FILE, CNV2[I]:5);
                        IF I MOD 16 = 0 THEN
                        WRITELN (CONV_FILE);
                END;
                BATCH_NO := BATCH_NO +1;

END;{if oar_option=m}


IF (OAR_OPTION = 'P') OR (OAR_OPTION = 'p') THEN
        {process CNV on the PC}
        BEGIN
        {remove the mean from data}
        MEAN (SAMPLES, VL);
        MEAN (SAMPLES, VR);
        MEAN (SAMPLES, HL);
        MEAN (SAMPLES, HR);
        MEAN (SAMPLES, CNV1);

        IF (OAR_INC = 'Y') OR (OAR_INC = 'y') THEN
        {call OAR procedure}
        OARM (SAMPLES,VL,VR,HL,HR,RAD,NEW_MONT,
        CNV1, SINGULARITY_DETECTED);

        FOR I := 1 TO SAMPLES DO
        CNV[I] := CNV1[I];

        IF NOT SINGULARITY_DETECTED THEN
        {if singularity is not detected in OAR
        process}
        BEGIN
                IF (FILTERING = 'F') OR
                (FILTERING = 'f') THEN
                {filter the CNV data}
                FILTER (SAMPLES, M, H, CNV);

                IF (BASE_LINE='B') OR (BASE_LINE='b')
```

```
                THEN
                {remove the base line from data}
                BAS_LNE (SAMPLES, NP1, NP2, NP3,
                NP4, CNV);

        FOR I := 1 TO SAMPLES DO
                {average the CNV data}
                        AVERAGE_CNV [I] := AVERAGE_CNV[I]
                        + CNV[I];

                        IF (SIN_TRI_OP = 'S') OR (SIN_TRI_OP
                        = 's') THEN
                        {if single trial file is required
                        then form the file}
                        BEGIN
                                FOR I := 1 TO SAMPLES DO
                                WRITE (SIN_TRI_FIL, CNV[I]
                                :12:8,' ');
                                WRITELN (SIN_TRI_FIL);
                        END;{if}
        END; {if not singularity detected}

        END; {oar on pc}
END

ELSE
BEGIN
                {skip the unwanted trial}
                FOR I := 1 TO SAMPLES DO
                READ (ORG_FILe, A,A,A,A,A,A,A,A,A,A,A,A
                        ,A,A,A,A,A,A,A,A,A,A,A,A);
        END;

END; {for n}


IF (OAR_OPTION = 'P') OR (OAR_OPTION = 'p') THEN
BEGIN

        FOR I := 1 TO SAMPLES DO
        BEGIN
                IF (DECISION = 'Y') OR (DECISION = 'y') THEN
                CNV[I] := AVERAGE_CNV[I] / TRIAL
                ELSE
                CNV[I] := AVERAGE_CNV[I] / TRIAL_NO
        END; {for i}


        FOR I := 1 TO SAMPLES DO
        BEGIN
                TIME := (I*12)/SAMPLES;
                        WRITELN (CONV_FILE,TIME:2:5,
                        ',CNV[I]:5:4);
                END {for i}
        END; {if}

CLOSE (ORG_FILE);
```

```
        CLOSE (CONV_FILE);
        IF (OAR_OPTION ='P') OR (OAR_OPTION ='p') THEN
        CLOSE (SIN_TRI_FIL);

        END; {convert procedure}

{=====================================}

{main section of the program}

BEGIN
        OPTION := 'R';
        REPEAT
                CLRSCR;
                GOTOXY (XP,YP);
                WRITELN ('Please enter:');
                GOTOXY (XP,YP+2);
                WRITELN (' "C" for MF Conversion or PC processing');
                GOTOXY (XP,YP+4);
                WRITE (' "E" to End');

                GOTOXY (XP,YP+6);
                WRITE ('option required ?  ');
                READLN (OPTION);
                IF (OPTION = 'C') OR (OPTION = 'c') THEN
                CONVERT;

                {declare the process is complete}
                SOUND (500);
                DELAY (1000);
                NOS   OUND;
        UNTIL (OPTION = 'E') or (OPTION = 'e')
END. {program proc}
```

Appendix D Listing of the Program Used to Obtain CNV Features From the Inter-Stimulus Interval Section of the CNV

```
PROGRAM ISIFEA;

{ Program Name: ISIFEA.PAS
 This program is used to extract features from the inter-
 stimulus section of the CNV.

 The features are obtained by averaging every 4 consecutive
 sample values in a section from sample number 174 to 237.
 This process produces 16 features.

 This program asks for:
 1) the name of a file for storing the CNV features
 2) the number of subjects to be included
 3) the names of the averaged preprocessed files.
}


CONST
        TRIAL_LENGTH = 1500;
VAR
        SAMPLE_NUMBER, SAMPLE, N, K, SUBJECT, SUBJ_NO :
        INTEGER;
        TIME, FEATURE : REAL;
        DATA : ARRAY [1..TRIAL_LENGTH] OF REAL;
        IN_FILE, OUT_FILE : TEXT;
        IN_FILE_NAME, OUT_FILE_NAME : STRING [12];

BEGIN
        WRITE ('Enter out-file name:  >  ');
        READLN (OUT_FILE_NAME);
        ASSIGN (OUT_FILE, OUT_FILE_NAME);
        REWRITE (OUT_FILE);
        WRITE ('Enter the number of subjects  >  ');
        READLN (SUBJ_NO);
        FOR SUBJECT := 1 TO SUBJ_NO DO
        BEGIN
                WRITE ('Enter in-file name  > ',SUBJECT:3,'  ');
                READLN (IN_FILE_NAME);
                ASSIGN (IN_FILE, IN_FILE_NAME);
                RESET (IN_FILE);

                {read the CNV samples}
                FOR SAMPLE_NUMBER :=1 TO TRIAL_LENGTH DO
                READLN (IN_FILE, TIME, DATA[SAMPLE_NUMBER]);

                {generate the CNV features}
                SAMPLE := 174;
                FEATURE := 0;
                FOR K := 1 TO 16 DO
                BEGIN
                        FOR N := 1 TO 4 DO
                        BEGIN
```

```
                        FEATURE := DATA [SAMPLE] + FEATURE;
                        SAMPLE := SAMPLE + 1;
                    END;
                FEATURE := FEATURE / 4;
                WRITE (OUT_FILE, FEATURE:9:4);
                FEATURE := 0;
                IF K=8 THEN
                WRITELN (OUT_FILE);
        END;

        WRITELN (OUT_FILE,'  ',IN_FILE_NAME);

        CLOSE (IN_FILE);
        END;
        CLOSE (OUT_FILE);

END.
```

Appendix E Procedure to Compute Correlation Matrix

If there are n individuals, and p variables (features) are obtained from the CNV response of each individual, The nxp data matrix can be represented by,

$$\mathbf{X} = \begin{bmatrix} x_{11} & x_{12} & \cdots & x_{1p} \\ x_{21} & x_{22} & \cdots & x_{2p} \\ \cdot & \cdot & \cdot & \cdot \\ \cdot & \cdot & \cdot & \cdot \\ \cdot & \cdot & \cdot & \cdot \\ x_{n1} & x_{n2} & \cdot & x_{np} \end{bmatrix}$$

where X_{ij} represents the value of variable j obtained from individual i.

The procedure for calculating the correlation matrix (R) is as follows:

i) The row vector of the means of X, denoted by $\bar{\mathbf{x}}$ (ie. the centroid) is computed using,

$$\bar{\mathbf{x}}' = \frac{1}{n} \mathbf{1}'\mathbf{X} \qquad \ldots(1)$$

where the row vector $\mathbf{1}'$ denotes a 1xn unit row vector (note the symbol ' indicates transpose).

ii) The mean corrected matrix $\mathbf{X}_d$ is determined by,

$$\mathbf{X}_d = \mathbf{X} - \mathbf{1}\bar{\mathbf{x}}' \qquad \ldots(2)$$

iii) The mean corrected sums-of-squares and cross-products matrix (S) is calculated using,

$$\mathbf{S} = \mathbf{X}'_d\mathbf{X}_d \qquad \ldots(3)$$

iv) The matrix whose entries along the main diagonal are the reciprocals of the square roots of the standard deviations of the variables in **X** is obtained. Let this matrix be $\mathbf{D}^{-\frac{1}{2}}$, therefore,

$$\mathbf{D}^{-\frac{1}{2}} = \begin{bmatrix} 1/\sqrt{s_{11}} & 0 & 0 & \dots & 0 \\ 0 & 1/\sqrt{s_{22}} & 0 & \dots & 0 \\ \cdot & \cdot & \cdot & \cdot & \cdot \\ \cdot & \cdot & \cdot & \cdot & \cdot \\ 0 & 0 & \cdot & \cdot & 1/\sqrt{s_{pp}} \end{bmatrix}$$

vii) The correlation matrix **R** can be found from pre- and post-multiplying **S** by $\mathbf{D}^{-\frac{1}{2}}$, ie.,

$$\mathbf{R} = \frac{1}{n-1} (\mathbf{D}^{-\frac{1}{2}} \mathbf{S} \mathbf{D}^{-\frac{1}{2}}) \qquad \dots(4)$$

Appendix F Listing of the Programs Used to Carry Out Cluster Analysis

Note:
P_1S_n = 1st Principal component for n^{th} schizophrenic patient
P_1N_n = 1st Principal component for n^{th} normal subject
P_1P_n = 1st Principal component for n^{th} PD patient
P_1H_n = 1st Principal component for n^{th} HD patient
P_1A_n = 1st Principal component for n^{th} AR OF HD patient

Appendix F1 Cluster Analysis of Schizophrenic Patients and Normal Subjects

```
NOTE
  20 SCHIZOPHRENIC PATIENTS
  FOLLOWED BY 20 NORMAL CONTROL SUBJECTS
  17 FEATURES
  PRIN1
END NOTE
READ DATA, VARIABLES CONTINUOUS 1, CASES 40
     P1S1
     P1S2
      .
      .
     P1S20
     P1N1
     P1N2
      .
      .
     P1N20
CLUSTER, METHOD WARDS, PRINT FUSIONS
TREE
STOP
```

Appendix F2 Cluster Analysis of Parkinson's Disease Patients and Normal Subjects

```
NOTE
  16 PARKINSON'S DISEASE PATIENTS
  FOLLOWED BY 16 NORMAL SUBJECTS
  17 FEATURES
  PRIN1
END NOTE
READ DATA, VARIABLES CONTINUOUS 1, CASES 32
     P1P1
     P1P2
      .
      .
     P1P16
     P1N1
     P1N2
      .
      .
     P1N16
CLUSTER, METHOD WARDS, PRINT FUSIONS
TREE
STOP
```

Appendix F3 Cluster Analysis of Huntington's Disease Patients and Normal Subjects

```
NOTE
  11 HUNTINGTON'S DISEASE PATIENTS
  FOLLOWED BY 11 NORMAL SUBJECTS
  17 FEATURES
  PRIN1
END NOTE
READ DATA, VARIABLE CONTINUOUS 1, CASES 22
     P1H1
     P1H2
      .
      .
     P1H11
     P1N1
     P1N2
      .
      .
     P1N11
CLUSTER, METHOD WARDS, PRINT FUSIONS
TREE
STOP
```

Appendix F4 Cluster Analysis of At-Risk of Huntington's Disease Patients and Normal Subjects

```
NOTE
  21 AR OF HD PATIENTS
  FOLLOWED BY 21 NORMAL SUBJECTS
  17 FEATURES
  PRIN1
END NOTE
READ DATA, VARIABLES CONTINUOUS 1, CASES 42
     P1A1
     P1A2
       .
       .
     P1A21
     P1N1
     P1N2
       .
       .
     P1N21
CLUSTER, METHOD WARDS, PRINT FUSIONS
TREE
STOP
```

Appendix G Listing of the Program Used to Obtain the CNV Amplitudes

```
PROGRAM CNVAMP;

{ Program name = CNVAMP.PAS.
  This program calculates the CNV amplitude from
  a preprocessed averaged CNV waveform.

  The CNV amplitude is calculated by averaging
  16 consecutive sample values prior to the
  imperative stimulus.

  This program asks for:
  1) the name of a file for storing the CNV amplitudes
  2) the number of subjects to be included
  3) the names of the files containing the averaged
     preprocessed CNV data
}


CONST
        TRIAL_LENGTH = 1500;

VAR
        SAMPLE_NUMBER, SAMPLE, N, SUBJECT, SUBJ_NO : INTEGER;
        TIME, FEATURE : REAL;
        DATA : ARRAY [1..TRIAL_LENGTH] OF REAL;
        IN_FILE, OUT_FILE : TEXT;
        IN_FILE_NAME, OUT_FILE_NAME : STRING [12];

BEGIN
        WRITE ('Enter filename for storing CNV amplitude >  ');
        READLN (OUT_FILE_NAME);
        ASSIGN (OUT_FILE, OUT_FILE_NAME);
        REWRITE (OUT_FILE);
        WRITELN;
        WRITE ('Enter the number of subjects >  ');
        READLN (SUBJ_NO);

        FOR SUBJECT := 1 TO SUBJ_NO DO
        BEGIN
                WRITE ('Enter input filename  > ',SUBJECT:3,'  ');
                READLN (IN_FILE_NAME);
                ASSIGN (IN_FILE, IN_FILE_NAME);
                RESET (IN_FILE);

                {calculate the CNV amplitudes}
                FOR SAMPLE_NUMBER :=1 TO TRIAL_LENGTH DO
                READLN (IN_FILE, TIME,
                DATA[SAMPLE_NUMBER]);

                SAMPLE := 222;
                FEATURE := 0;
                FOR N := 1 TO 16 DO
```

```
                BEGIN
                FEATURE := DATA [SAMPLE] +  FEATURE;
                SAMPLE := SAMPLE + 1;
            END;
        FEATURE := FEATURE / 16;

            WRITE (OUT_FILE, SUBJECT:5,'  ', IN_FILE_NAME);
            WRITELN (OUT_FILE, ' CNV AMP =  ', FEATURE:9:4);

            CLOSE (IN_FILE);
    END;
    CLOSE (OUT_FILE);
END. {cnvamp}
```

Appendix H Documentation

The method and the procedure for generating the results included in this thesis are described in detail in the relevant chapters. Some operations which were not directly related to the techniques involved but they had to be carried out to obtain the test results are not included in the main text of this thesis. They are described in this Appendix.

The CNV data for each subject and the reaction times for that subject were held in the same data file. All data files were stored on cassettes. It was necessary to transfer the data files from the cassettes to the hard disk of the PC. The method followed was similar to that for transferring data from the PC to the cassettes and it required the use of a commercially available tape streamer called SYSGEN and a program called FBACK. These are described in chapter 3 (section 3.15).

Once the data files were on the hard disk they were processed by either the PC or they were transferred to an IBM mainframe computer. The PC was connected to the mainframe computer by a wire link.

H1 Documentation for Chapter 7

The test results included in chapter 7 were obtained by using a number of programs on the mainframe computer. These programs were either written by Nichols [1982] and Coelho [1988] or they were commercially available programs. Therefore the data files had to be transferred to the mainframe computer for the required analysis. In order that this data transfer can take place correctly the format of the data files had to be changed from binary to ASCII. This was achieved by using one of the options available in the Turbo Pascal Program PROC.PAS (see Appendix C for the listing of this program). The data transfer from the PC to the mainframe computer was carried out using a commercially available program called MS-DOS Kermit [MS-DOS KERMIT, 1988]. A full

description of the steps necessary to ensure the data transfer from a PC to a mainframe computer is provided in MS-DOS Kermit [1988]. Coelho [1986] produced a report which indicated the steps necessary to run his (and Martin Nichols') programs on the mainframe computer. Those steps were followed. The operations performed by the execution of those steps were described in detail in chapter 7 and they resulted in the test results included in chapter 7.

H2 Documentation for Chapter 8

By looking at the hardcopy of the data recordings (this was produced by the EEG machine during the data recordings) 8 CNV trials not grossly contaminated by ocular artefact were identified for each subject. One of the options available in the Turbo Pascal program PROC.PAS (see appendix C for the listing of this program) enabled the preprocessing of the CNV data as described in chapter 6. The preprocessed CNV waveforms were also averaged by the program PROC.PAS. Sixteen features were extracted from the inter-stimulus interval section of each preprocessed averaged CNV waveform as described in chapter 8 by using the Turbo Pascal program ISIFEA.PAS. A listing of this program is included in Appendix D. A 17^{th} feature which was the time difference between the onset of the imperative stimulus and the CNV returning to its baseline was obtained manually as described in chapter 8. The selected features were normalised using the formulae given in chapter 8. They were then used in a commercially available neural network package called NeuralWorks [1988]. The method of using NeuralWorks is provided in NeuralWorks Manual [1988]. The details related to the implementation of the neural networks are included in chapter 8.

H3 Documentation for Chapter 9

Seventeen features were obtained from preprocessed averaged CNV waveforms of the subjects as described in Appendix H2 (these feature were not normalised for

the analysis carried out in chapter 9). A file was formed containing the 17 features for the subjects in a patient category (such as schizophrenic patients) and their normal control subjects. A similar file was formed for each of the other patient categories (ie. Parkinson's disease, Huntington's disease, and at-risk of Huntington's disease) and their normal subjects. These files were transferred to the mainframe computer using MS-DOS Kermit [1988] and were analysed by a number of software packages described in chapter 9. These generated the principal component analysis and cluster analysis results included in chapter 9.

The CNV amplitude results were obtained from the preprocessed averaged (over 8 trials) CNV waveforms using a program called CNVAMP.PAS. A listing of this program is provided in Appendix G. The CNV amplitudes were then transferred to the mainframe computer for analysis by various software packages described in chapter 9.

H4 Documentation for Chapter 10

One of the options available in the Turbo Pascal program ACQ.PAS (see Appendix A for its listing) read from the data files the values of the reaction times for each subject and produced an averaged reaction time value. The averaged values of the reaction times for the subjects were transferred to the mainframe computer using MS-DOS Kermit and were analysed by the software packages described in chapter 10.

References

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4. A PC-based instrument for recording CNVs. **R. Saatchi. B.W. Jervis Sheffield City Polytechnic, Sheffield.**

A modular, multi-purpose instrumentation system for recording CNV responses has been developed and is now in use. It comprises an IBM PC, a signal conditioning box, a stimulator, a timing and interface section, and an EEG machine.

The system can acquire up to 20 Mbytes of data from 8-analogue channels whilst storing them at pre-defined intervals onto the PC hard disk. The data can then be displayed on a VDU or can be processed by various programs. A tape streamer facilitates the down-loading of the data from hard disk to tape for permanent storage.

The special features of this system are:

(i) it controls the production of stimuli according to the stimulus paradigm chosen; and

(ii) it has an automatic gain control circuit to enhance the accuracy of A/D conversion for each sample by fully utilising the dynamic range of the A/D converter which is particularly useful as EEG signals can vary from a few μ V to several hundred μ V, when contaminated by ocular artefacts.

Special consideration was also given to the problems of noise and drift.

The instrument detects false CNV responses and a pause switch enables the sampling to be halted temporarily. The sampling rate can be altered through software. Beside EEGs, the system is being used to measure electro-oculograms, reaction times, ECGs and the PGR.

the instrument may be reprogrammed to measure other types of EEG response.

IEE Colloquium on PC-Based Instrumentation, Digest no: 1990/025 (31 January 1990, London).

An integrated system for process control and the acquisition storage, and processing of data

B W Jervis and R Saatchi

1.0 Introduction

The system was developed to automate a programmable experimental stimulus paradigm and to record the resulting eight analogue signals and to enable subsequent signal processing. The recorded signals consisted of an EEG, some EOGs, an ECG and the PGR (psychogavanic sway) of a subject who was required to respond by pressing a button. The signals were to be cross correlated so simultaneous sampling was necessary. Both continuous and discontinuous recordings were required. Erroneous responses were to be discarded and the reaction time to button press was to be measured. A/D overload was to be avoided and the A/D converter sensitivity was to be maximised. The system was required to communicate with a mainframe computer. It was to be compatible with an EEG machine. The resultant design had to have general application with some software and hardware modification as necessary.

2.0 Requirements

All the present requirements (control, recording, and processing etc.) can be achieved using a PC plus signal conditioning electronics. An EEG machine was incorporated to satisfy the clinicians. The parts cost excluding the EEG machine will be about £5000.

3.0 System block diagram

The signals after amplification by 50 by the EEG machine are high-pass filtered (fc=0.0159Hz), amplified by 80, low-pass filtered (fc=30Hz) and are fed to sample and hold units, see figure (1). The multiplexed signal is fed into both a window detector and the A/D card to be digitized. The click/tone generator provides the necessary acoustic stimuli. The bode plots of the complete sytem are shown in figure (2).

4.0 Memory requirement for recording and data storage

Using sampling rate fs of 125Hz, 8 channels, trial length 12 seconds consisting of experimental paradigm for CNV recording 1 second pre-stimulus, 1 second inter-stimulus-interval (ISI), 10 seconds post-stimulus, repeated 32 times for evey subject and considering three bytes per sample (2 bytes A/D output and a byte for the PGA gain), and 2 bytes per trial for reaction time then a trial requires 36002 bytes of RAM. For 32 trials the minimum data storage requirememt is 1.125MBytes per subject.

Department of Electrical and Electronic Engineering, Sheffield City Polytechnic.

5.0 Pre-processing

5.1 Amplification by EEG machine

The signals are amplified by 50 at the EEG machine by differential amplifiers which have CMMR of 1000:1. Differential recording is used for compatibility with the differential measurements between electrode pairs and to attenuate common mode noise.

5.1 High pass filtering

Low frequency high pass filtering is carried out to remove the DC drift [1]. The filter time constant should be at least three times the duration of the signal of interest, here the 1s inter stimulus interval, ISI [2]. A simple CR circuit with C=1uF and R=10MΩ provides a 10s time constant. Being a first order single-lag circuit it has a constant gain above fc=0.0159Hz and constant phase shift above 0.159Hz. The CNV response has a fundamental harmonic at about 1Hz, other EEG components of interest lie at higher frequencies and most EOG frequency components will be above 0.159Hz. The CR circuit will therefore not distort the signals in the frequency range of interest.

5.2 Instrumentation amplifiers (IAs)

The IAs used are based on the INA110KP IC from BURR-BROWN. INA110KP has a CMMR of about 106dB and has very low drift and fast setting time (4μs to 0.001%). A gain of 80 was used in order to have a total signal amplification of 4000 (ie 50 x 80) at the A/D card. This allows use of the ±20mV input of the A/D converter.

5.3 Low pass filtering

Low-pass filtering is used to prevent aliasing. The filter is required to have a sufficiently steep roll-off to avoid aliasing combined with a sufficiently linear phase to prevent distortion. A cut-off frequency of 30Hz was chosen which exceeded the highest frequencies of interest and which would also attenuate any 50Hz mains noise. The sampling frequency was 125Hz. A fourth order Bessel low-pass filter provided the necessary roll-off and phase linearity. The attenuation (dB) at frequency f is given by [3];

$$a(f) = 20 \log_{10} \frac{1}{s^4+10s^3+45s^2+105s+105}$$

where s = f/fc. So for fc = 30Hz and the largest aliasing component at f = 95Hz, s = j95/30 = j3.167. This gives a(95) of about -47.87dB and an aliasing voltage of 4.08mV ie an error of 0.408% which is considerd acceptable. This filter design was based on the Sallen-Key equivalent circuit [4] using TL0741CP IC unit.

5.4 Sample and hold (S/H)

The duration of the sample and hold period for every sample is 8mS ie 1/125s. The LF398 S/H units used are of ultra-high DC accuracy with fast signal acquisition and low droop rate. The S/H capacitor used is of the polystyrene type with a value of 0.01μF. With this capacitor and available sample time of 1mS, the droop rate is about 0.083mV/s giving a negligible error during A/D conversion cf aliasing error of 0.4%. Simultaneous sampling ensures that the time phase relationship of the signals is preserved during multichannel sampling [5].

5.5 Multiplexing

An analogue multiplexer (HI506) was used after the S/H so that only one A/D, programmable gain amplifier and window detector was necessary. The required multiplexing rate was 1000, ie 8 x 125. The multiplexer on the A/D board could not be used as it was not possible to connect its output to the window detector.

5.6 Analogue to digital conversion

A commercially available board from the DT2801 series was used to digitize the signals [6]. This board has a programmable gain amplifier and a 12 bit A/D. The error of the 12 bit convertor at mid range is 0.02%. This is much smaller than the aliasing error of 0.40%. The signal varies from $\pm$5uV to $\pm$1mV ie a factor of 200 or a dynamic range of 46.02dB. Since the four A/D card input ranges are from $\pm$20mV to $\pm$10V ie a factor of 500 or 54dB, therefore the PGA ensures effective use of the A/D converter. The dynamic range of A/D is 72dB which therefore is ample.

The PGA which lies before the A/D converter provides the third stage of signal amplification. The gain of the PGA can be set to either 1, 10, 100 or 500 through software. The value of gain chosen is determined by a window detector. The window detector consists of three comparators. The output of each comparator changes with the signal voltage and so indicates signal voltage range. The window detector is located in the signal conditioning unit. The interfacing of the window detector and multiplexer to the PC was realised by employing an INTEL 8255A programmable peripheral interface device.

6.0 Computer system

The computer used was an IBM PC AT (E) which has a clock rate of 6MHz, 640MByte RAM, 20MByte hard disk and a tape streamer. It has several expansion slots two of which were used for A/D card and VERO-ELECTRONICS card. The PC communicated with an IBM mainframe via a RS232 port and a KERMIT link.

7.0 Continuous recording

This was realised by using one of the direct memory access controllers (DMAC) of the PC to transfer the digitized data to a page in RAM. Once half that page is full another DMAC transfers the completed half page to hard disk while the second half is being completed. The function of PC μP (INTEL 80286) is to supervise the data transfer. After a page is transfered, the first DMAC continues writing into the first half of that page and procedure is repeated. The number of bytes forming a page is 64Kbyte. The A/D thoughput to the system memory using the DMAC is 6000 samples per second.

8.0 Transfer to back-up tape

Data transfer from hard disk to tape is controlled by a program called FBACK from SYSGEN, INC. The PC was fitted with a SYSGEN SMARTIMAGE tape drive. A 20Mbytes cassette fitted into the tape drive can receive the full contents of the hard disk (transfer time about five minutes).

9.0 Control of integrated system

To provide the timing information, two programmable interval timers (INTEL 8254) were used as shown in figure (3). Each timer contains three counters which can be programmed separately. The PC itself has a similar timer but it could not be utilised as it is dedicated to the PC. To add the timers to the PC a prototype board was obtained (from VERO-ELECTRONICS LTD). The board includes address decoding circuitry and the timers were soldered on to it.

10.0 Plotted recordings

Figure (4) shows a plot of vertical right EOG. A single CNV trial is shown in figure (5) and that of the averaged processed CNV is shown in figure (6). Figures (7) and (8) show the plots of ECG and PGR respectively.

11.0 Conclusion

The system works satisfactorily, is relatively cheap, and is adaptable.

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[5] BURR-BROWN (1986), "The handbook of personal computer instrumentation", Watford, England.

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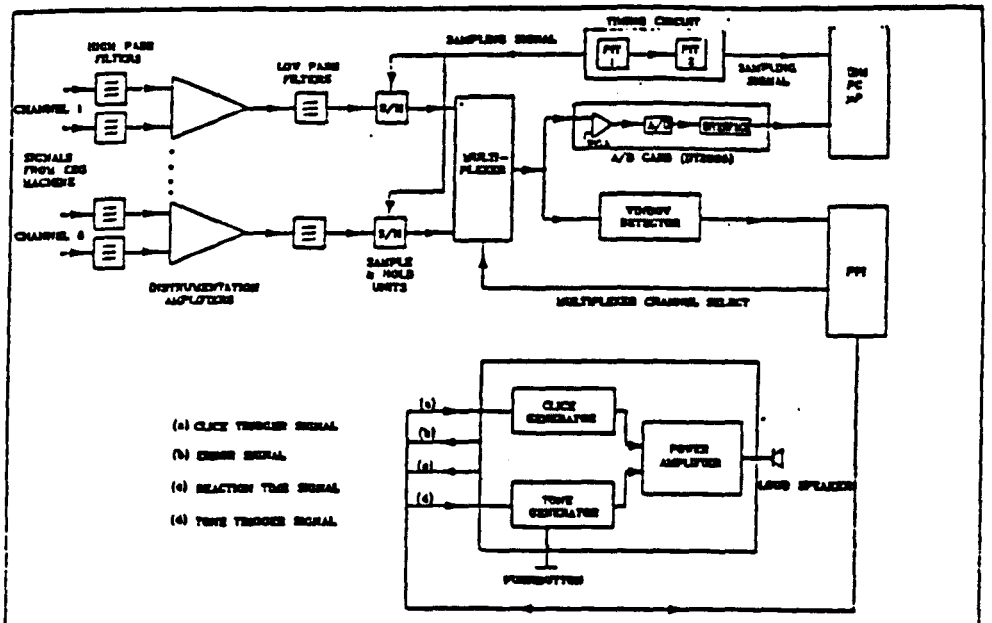
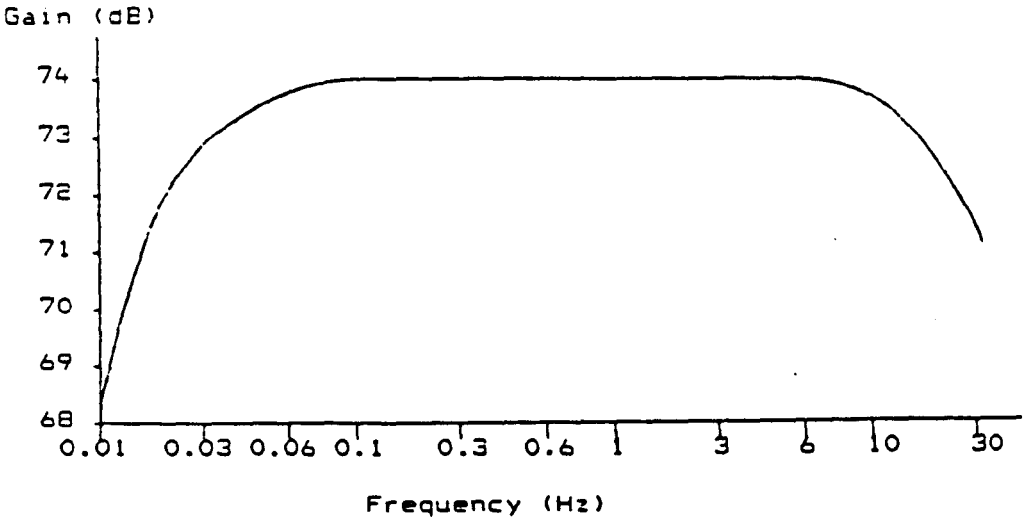
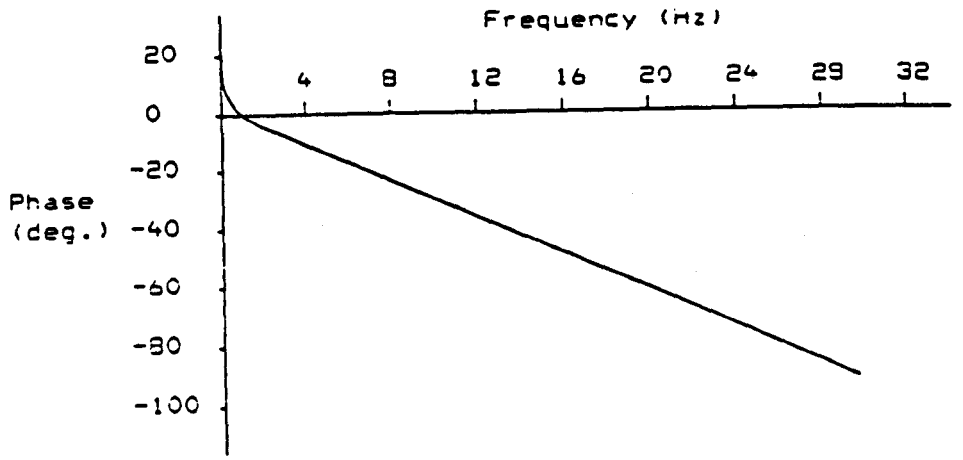


Figure (1) System Block Diagram



(a) Gain/frequency response



(b) Phase/frequency response

Figure (2) System bode plots

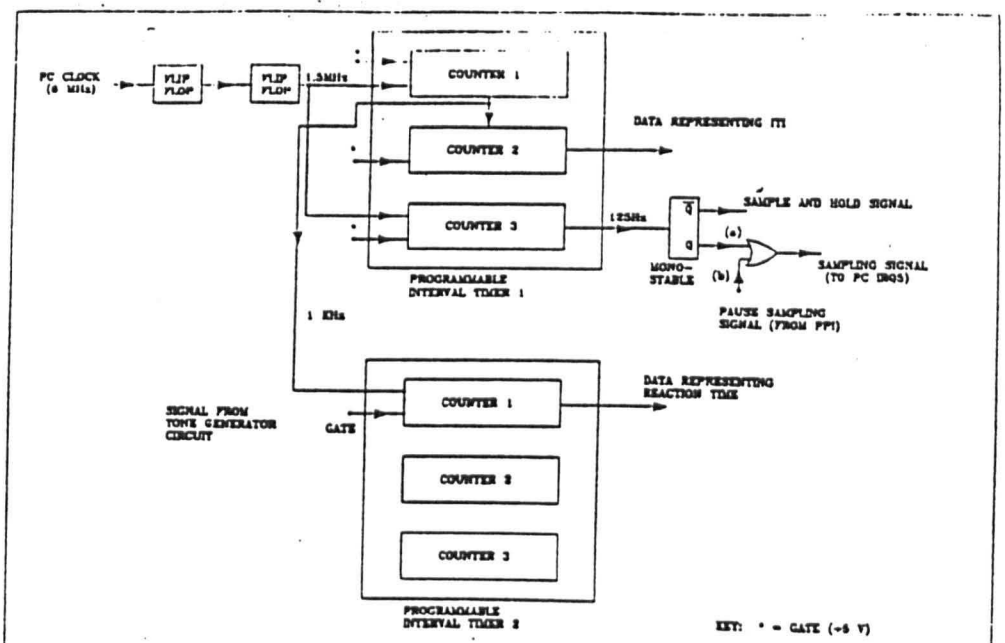


Figure (3) System timing circuit

Figure (4) EOG signal (vertical right)

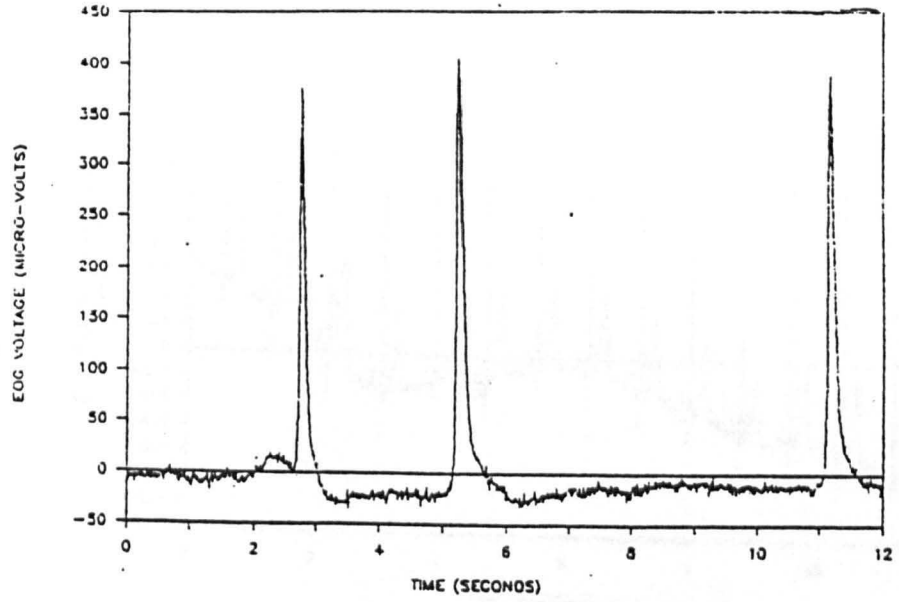


Figure (5) Unprocessed CNV response

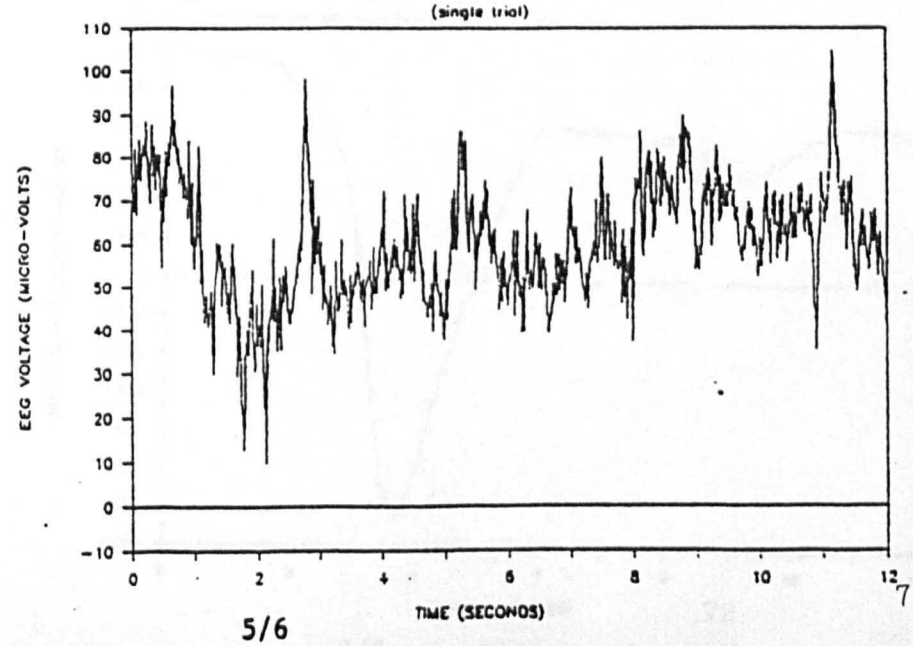


Figure (6) A processed CNV response

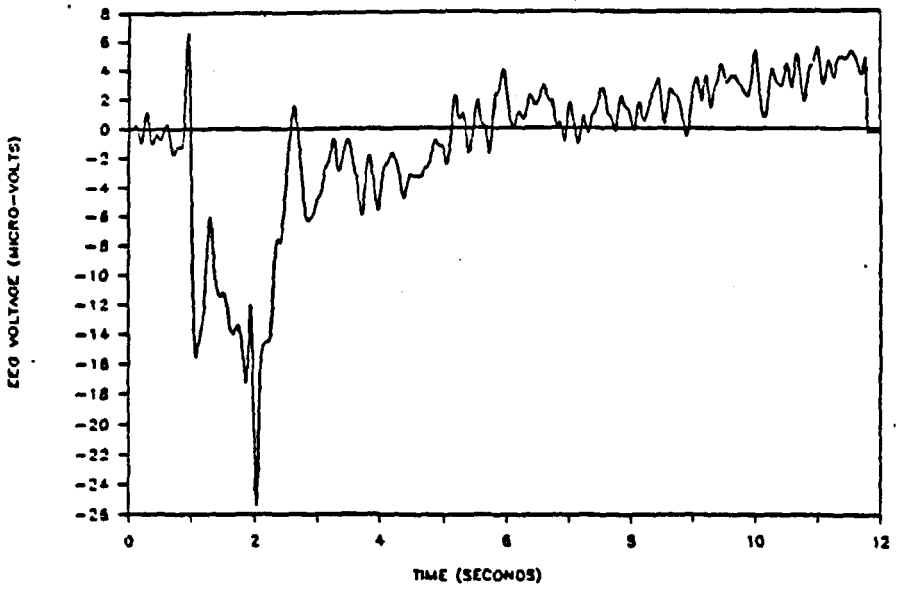


Figure (7) ECG signal

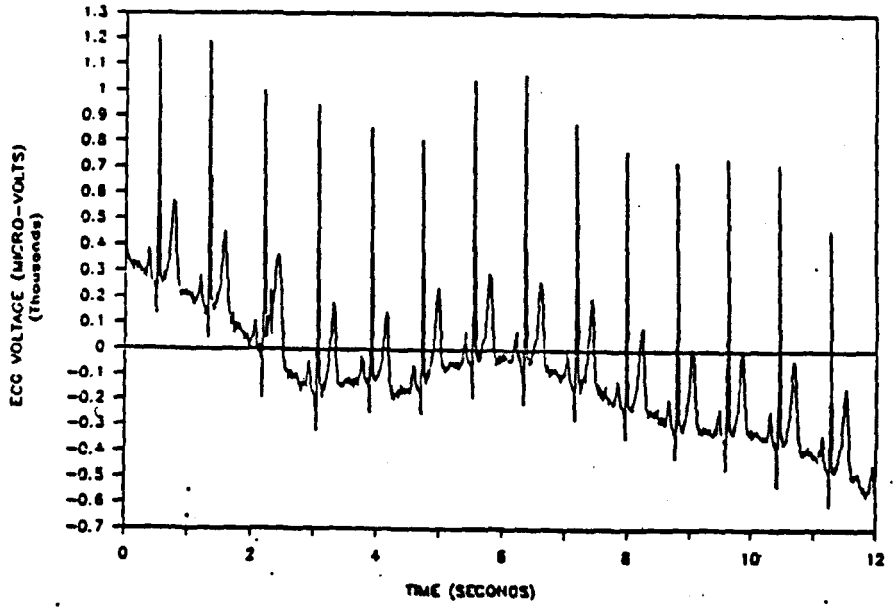
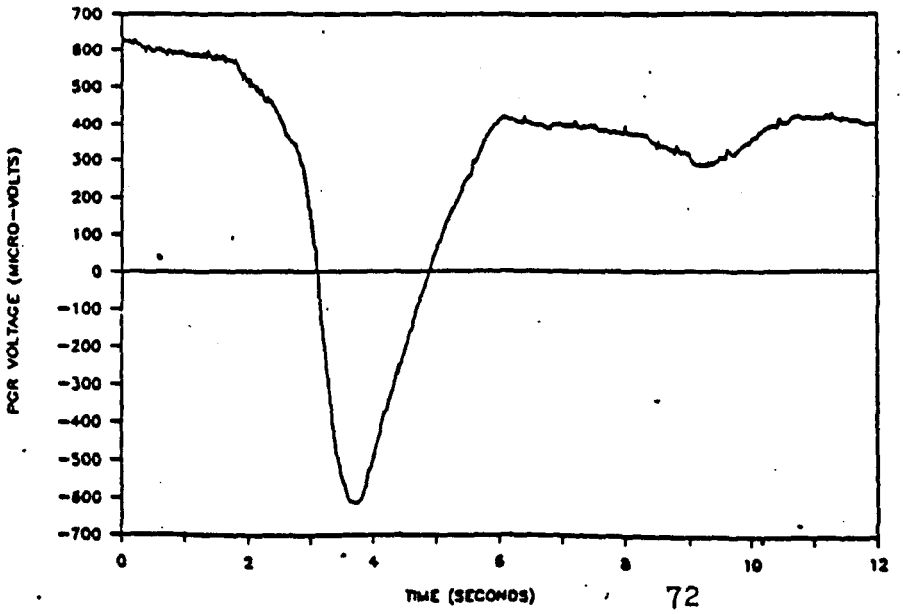


Figure (8) PGR signal



Proceedings of the Physiological Society Held at Sheffield University (19-20 April 1991).

C 52

Computerised diagnosis of schizophrenia, Huntington's disease and Parkinson's disease in man using the contingent negative variation (CNV)

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The aim of the investigation was to discover whether Schizophrenia, Huntington's disease(HD), and Parkinson's disease(PD) could be diagnosed by analysing the CNV.

With the local ethical committee's approval, the CNVs of 112 subjects in the above named categories and their age/sex matched normal controls were obtained. The CNV trials were preprocessed by a procedure which carried out mean level removal, base line correction, ocular artefact removal and digital filtering. The 500 ms of data preceding the onset of the warning stimulus (S1) and imperative stimulus (S2) from each preprocessed CNV trial were windowed by a Kaiser Bessel window and then Fourier transformed. To generate the discriminatory statistical variables, statistical tests (Jervis *et al.* 1984) were applied to the first six Fourier harmonics of the CNV. These tests were designed to investigate the amplitude and phase spectra of the selected lengths of pre- and post stimulus recording. The resulting data were used in a discriminant analysis (DA) routine in two stages. Initially the variables of the known subjects were processed by DA. This resulted in the setting up of a classification rule. Then the DA was used to diagnose the unknown subjects on the basis of the classification rule and the statistical variables. The results indicate that it is possible to distinguish the patients from the matched normal controls accurately.

Neural networks and clustering techniques were also applied to the CNV using the features obtained in the time domain. The results were in agreement with those of the discriminant analysis. It was also observed that with the clustering technique, it may be possible to presymptomatically diagnose HD.

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Proceedings of the British Society for Clinical Neurophysiology held at the Royal London Hospital London (18 October 1991).

9. **An investigation of presymptomatic diagnosis of Huntington's disease using the contingent negative variation.** - B.W. Jervis, M.R. Saatchi, E. Allen, N. Hudson and S. Oke (Sheffield City Polytechnic, Sheffield)

Several studies have concluded that the contingent negative variation (CNV) is affected in Huntington's disease (HD) patients. In this investigation the CNV responses were analysed with the aim of presymptomatically diagnosing HD. A set of time domain features was obtained from the preprocessed, averaged CNV responses of HD patients (n=11), and 'at-risk' of HD patients (n=21) and their age/sex matched normal control subjects. The features were used in Ward's hierarchical clustering method.

Initially the HD patients and their normal control subjects were analysed. This indicated the method could differentiate between the CNV responses of the HD patients and their normal control subjects. Then the 'at-risk' of HD patients and their normal control subjects were analysed. The method identified 8 'at-risk' of HD patients as having abnormal CNV responses. As the 'at-risk' of HD patients did not have any disorder which could have affected their CNV responses, except being 'at-risk' of HD, the conclusion was that the 8 'at-risk' of HD patients had a higher chance of developing HD compared to the remaining 'at-risk' of HD patients.

t-tests were also carried out. They indicated the CNV amplitudes of the 8 'at-risk' of HD, identified as having abnormal CNV responses, were significantly reduced compared to their normal control subjects and the remaining 'at-risk' of HD patients.

The effectiveness of the method needs to be evaluated further but if proved effective could be useful in presymptomatically diagnosing HD in cases where the genetic testing method could not be used (i.e. where the suitable family members are not available).

PC-based integrated system developed to diagnose specific brain disorders

A PC-based instrumentation system developed primarily to diagnose Huntington's disease, Parkinson's disease and schizophrenia by using the contingent negative variation (CNV) of the subject's electroencephalogram (electrical activity of the brain) is described. The system is capable of controlling the required experiment, acquiring and processing the signals from eight channels, and generating the diagnosis results. As the diagnosis was based on a signal (i.e. the CNV) which has an amplitude typically of the order of a few microvolts and is usually badly contaminated by various noise sources, considerable and accurate signal conditioning and preprocessing was necessary. A description of the steps following from the data recording to produce the diagnosis results is provided.

by M. R. Saatchi and B. W. Jervis
Sheffield City Polytechnic

The study of electrical activity of the brain has contributed to the better understanding of cerebral physiology and to the ability to assess subjects with known or suspected disorders of brain function.[1-7] The first reported observation of brain electrical activity was made by a British physiologist called Caton.[8] He provided the following description about his finding in the British medical journal: 'The external surface of the [brain's] grey matter is usually positive in relation to the surface of the section through it. Feeble currents of varying direction pass through the multiplier when the electrodes are placed on two points on the [brain] external surface, or one electrode on the grey matter, and one on the surface of the skull.'

Caton's investigations were carried out on the brains of rabbits and monkeys. However, it was not until 1929 that Berger[9] discovered the electroencephalogram (EEG) in man by using a galvanometer connected to electrodes attached to the scalp. Technological advances in 1930s made it possible for the brain electrical activity to be amplified and displayed on a cathode-ray tube. The resulting waveforms could be photographed for a permanent record. These early amplifiers were usually AC coupled and often suffered from pick-up of external interference.

During the 1940s pen recorders became available and for the first time electroencephalogrammers could have an immediate permanent record of the brain electrical activity. The developments in the recording and analysis of EEGs led to the observation of event-related potentials. An event-related potential (ERP) is the brain electrical activity that occurs in association with the eliciting event. The contingent negative variation (CNV) is an ERP first reported by Walter *et al.*[10] The number of articles about the CNV exceeds 800. A review of them indicates that the CNV is a potentially useful measure of brain behaviour function. Tecce and Cattanach[11] and McCallum[12] discuss the nature of the CNV and some of its applications. The CNV has been found to be valuable in the study of ageing and dementia, the effects of drugs, and psychopathology.

The CNV is a negative shift in the EEG potential measured on the scalp and compared to the potential of an electrical reference electrode placed on a suitable site such as the earlobes. In our experiments, two channels of CNV recording were obtained by electrodes located one at the vertex (top of the head) and another close to the vertex. Both electrodes used a common reference obtained from a pair of connected electrodes on the left and right earlobes. A schematic CNV waveform is shown in Fig. 1. The CNV elicitation involves the generation of a warning stimulus S1 (selected to be a click) to warn the subject of the upcoming imperative stimulus S2 (selected to be a tone). The time interval between the onset of S1 and S2 is called the inter-

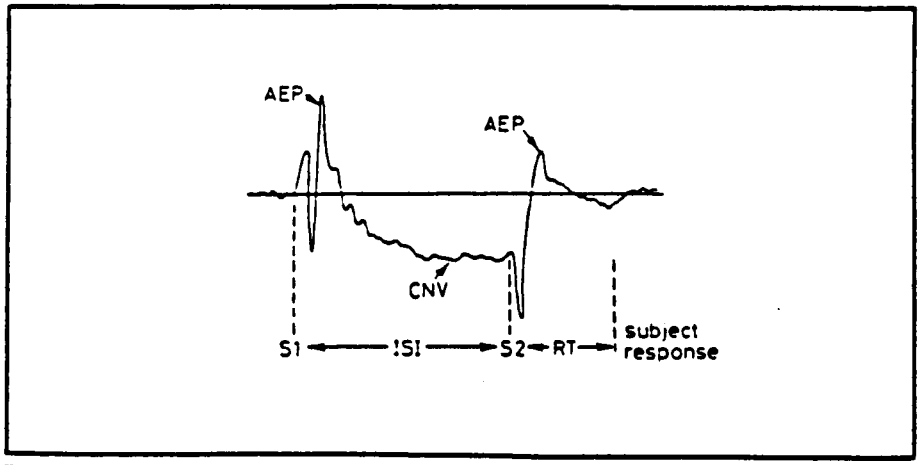


Fig. 1 Schematic diagram of a CNV waveform

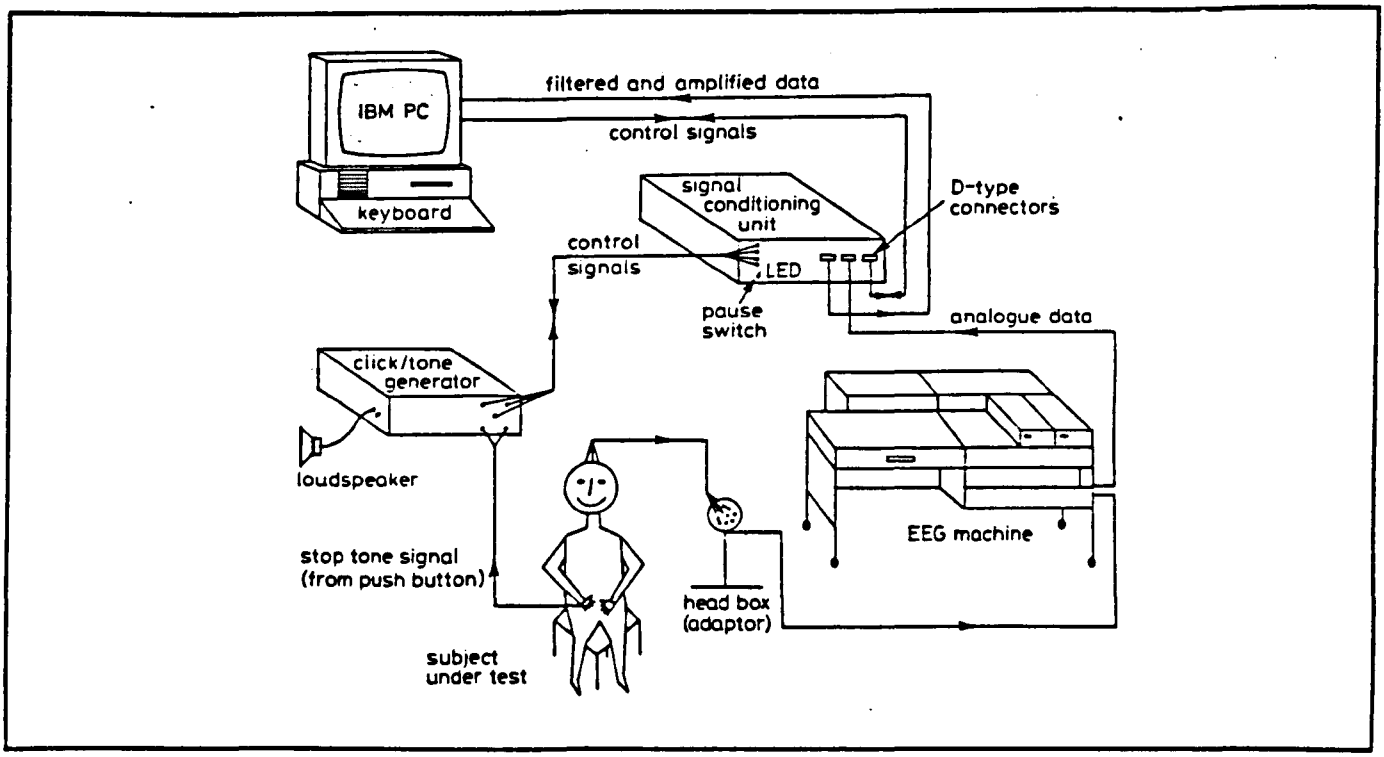


Fig. 2 System set-up during a data recording

stimulus interval (ISI) and was chosen to be 1 s.

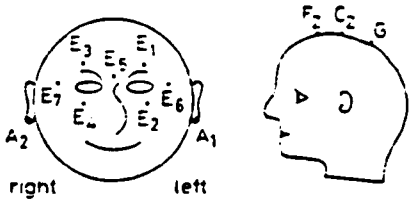
The subject under test is asked to stop the tone as soon as possible by pressing a hand-held pushbutton. The negative shift in the EEG follows S1 and after the subject has responded it returns to the baseline. The time taken between the generation of S2 and the subject's response is the reaction time (RT) and was measured. The spike-like waveforms immediately following S1 and S2 (duration about 0·3 s) are generated as a result of the onset of the stimuli (S1 and S2). They are referred to as auditory-evoked potentials.

A CNV waveform could be considered as consisting of three sections, pre S1, ISI and post S2. Although the actual CNV lies in the ISI section, the recording of pre S1 and post S2 sections is necessary in order to be able to carry out the required preprocessing procedure. A CNV record contained the waveforms generated by 32 trials separated by a random interval called inter-trial interval (ITI) which was selected to vary between 100 ms and 500 ms.

The CNV waveform is susceptible to contamination by the much larger background EEG and ocular artefact (OA) potentials.[13-15] The positive cornea and the negative retina form an electrical dipole so that, whenever this field is changed due to eye rotation or eye lid movement, a change of potential develops around the eye. This potential is referred to as electro-oculogram (EOG) and it spreads across the scalp to contaminate the EEG. The term OA is a collective reference to a number of eye-related potentials observed in the contaminated EEG. By recording the appropriately selected EOG signals and carrying out the necessary OA removal process, it is possible to reduce the amount of OA in the recorded CNV responses.

The recording of electrocardiogram (ECG) and psychogalvanic response (PGR) were also included. They enabled the monitoring of the subject's heart rate and the skin resistance, respectively. Following a warning stimulus, the heart may briefly decelerate[16] and the PGR amplitude of the subjects with depression has been found to be smaller compared with that of normal control subjects.[17]

Commercially available equipment was available which could record the signals of interest, but its cost was too high (about £20 000), it had little data-processing capability and it could not provide many of the desired features indicated in the next section.



Channel number	Function	Electrode position
1	vertical left EOG	E_1-E_2
2	vertical right EOG	E_3-E_4
3	horizontal left EOG	E_5-E_6
4	horizontal right EOG	E_5-E_7
5	CNV C_z	C_z Ref. A_1/A_2
6	CNV F_z	F_z Ref. A_1/A_2
7	ECG	—
8	PGR	—

Fig. 3 Electrodes' sites

Therefore it was decided to design and construct a PC-based system which could control the experiment and accurately carry out the recording, storage and preprocessing of the data and generate the diagnosis results.

Specifications

The system was required to carry out the simultaneous sampling of the signals from eight analogue channels with a sampling rate of 125 Hz and to generate the necessary stimuli required for the elicitation of the CNV. It had to measure the subject's reaction time (RT) to the imperative stimulus (S2) and time the random time interval between the successive CNV trials.

The signals of interest were: the CNV of EEG obtained from two sites, the EOG from four sites, the ECG and the PGR. The maximum signal voltage gain was 2×10^6. To increase the analogue-to-digital conversion accuracy, a programmable gain amplifier (PGA) was necessary prior to a 12 bit analogue-to-digital (A/D) convertor. The gain of this PGA varied in accordance with the signal amplitudes.

It was important not to distort the signals during the acquisition or conditioning and to ensure the patient's safety during the recording. Online paper chart recording of the signals was required, as it would enable the technician recording the data to mark off any important event (which affects the recording) on the chart and to continuously monitor the recording. The system had to be able to store a large amount of data, to process and analyse it, and then to provide the diagnosis results.

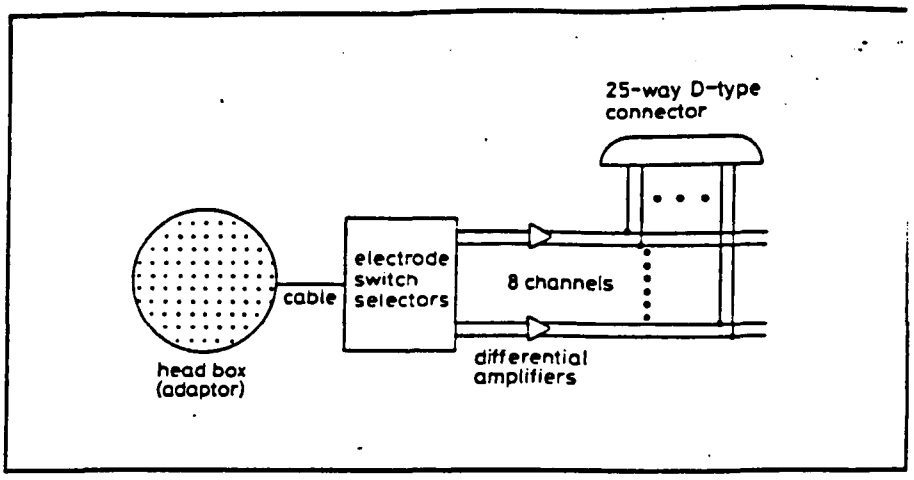


Fig. 4 Diagram of the EEG machine input section

Hardware

The system consists of an IBM PC (AT model, having a 20 Mbyte hard disc and fitted with a Sysgen tape streamer), an Elema-Schönander EEG machine, an acoustic stimulator device, and a signal-conditioning unit. The set-up of the system during a recording is shown in Fig. 2. The CNV and EOG signals were obtained from the sites shown in Fig. 3. The ECG and PGR were taken from the subject's wrist and hand, respectively.

The signals from the appropriate electrodes (for CNV and EOG recording, the electrodes used were DC silver/silver-chloride electrodes) were fed via the EEG machine adapter (head box) into the electrode selector switches (which enables the setting of the recording montage) and the differential amplifiers of the EEG machine as shown in Fig. 4. These differential amplifiers had a fixed gain of 50. The signals to be digitised were then taken from the differential amplifiers at the output of the EEG machine. In this way the EEG machine produced the required paper chart of the signals as usual and the signals were also conditioned, digitised and stored by the following hardware units.

Fig. 5 shows the sections of the hardware following the EEG machine.

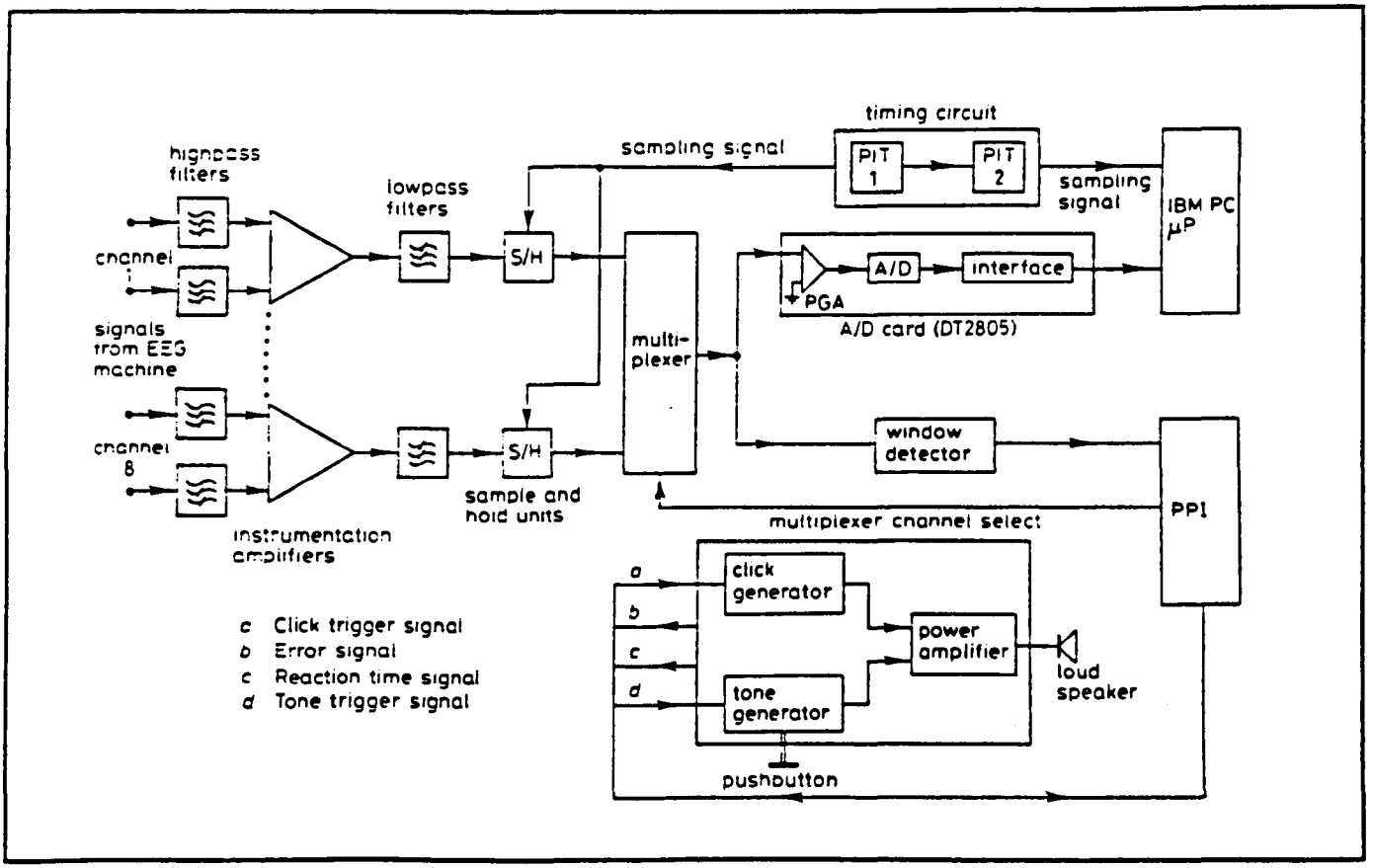


Fig. 5 Hardware units following the EEG machine

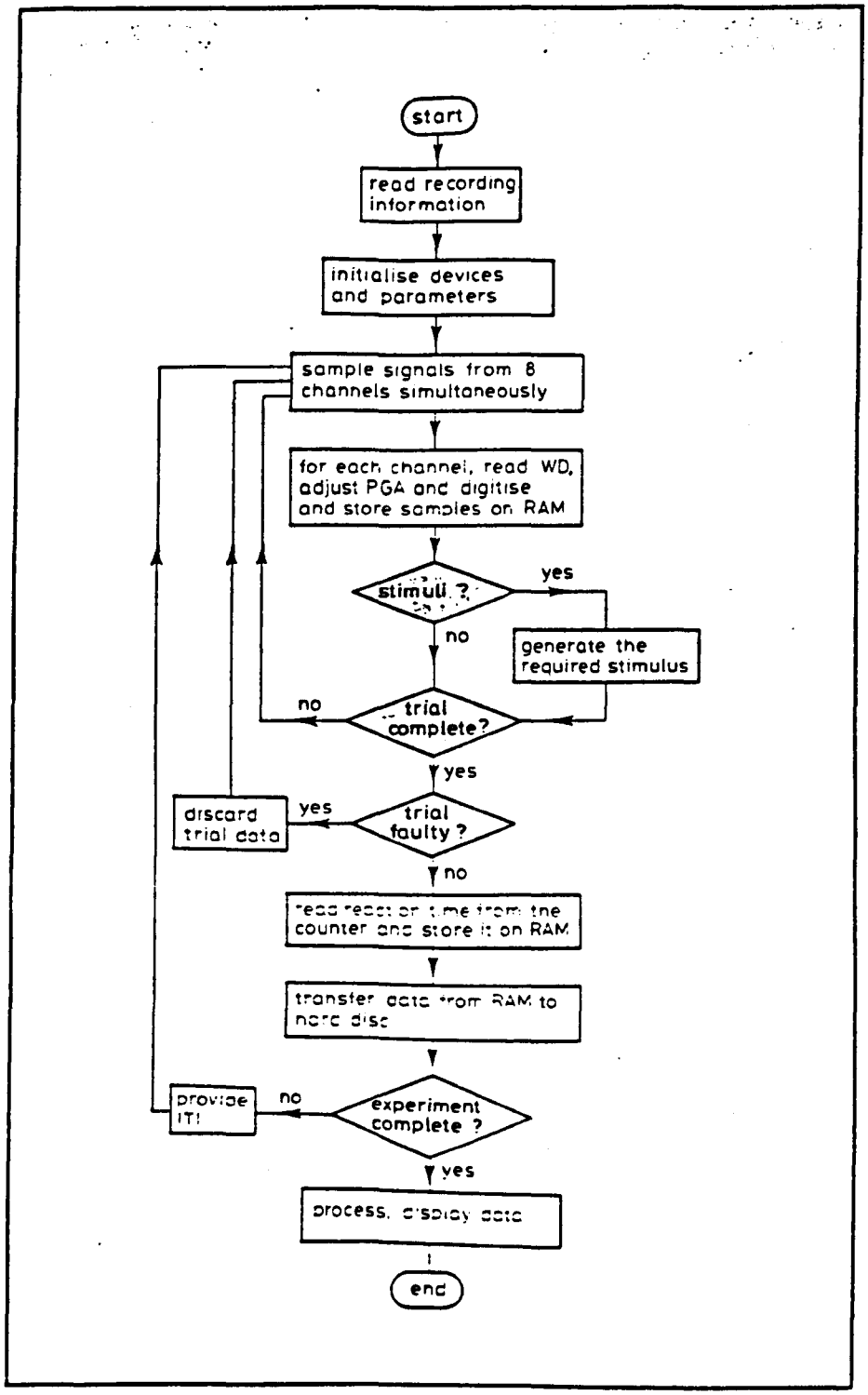


Fig. 6 Data recording software flow chart

Highpass filtering was carried out to minimise the DC drift. The DC drift is mainly due to the extracerebral potentials and can be several millivolts.[16] The highpass filter time constant should be at least three times the duration of the CNV's ISI (which was chosen to be 1 s) otherwise the CNV waveform would be distorted.[16] A simple *CR* circuit with $C = 1\mu F$ and $R = 1M\Omega$ provided a 10 s time constant.

Following the highpass filters are the instrumentation amplifiers which convert the signals to unbalanced form. The instrumentation amplifiers used were based on the INA110KP device from Burr-Brown.[19] This amplifier has a CMRR of about 106 dB, low drift and fast settling time. A gain of 42 was chosen for this stage. This resulted in a total fixed voltage amplification of 4000 at the A/D card, i.e.

total fixed voltage gain =
$50 \times 42 \times 1{\cdot}9067 = 4000$

where the factor of 1·9067 represents the gain of the lowpass filter described below.

Lowpass filtering was necessary to prevent aliasing. The filter had to be chosen such that it provided both a linear phase response in order to avoid phase distortion and a sufficiently steep gain roll-off. A cut-off frequency of 30 Hz was chosen which exceeded the highest frequency of interest and which would also attenuate any 50 Hz mains interference. A fourth-order Bessel lowpass filter satisfied the above requirements.[20] This lowpass filter design was based on the Sallen and Key equivalent circuit[21] using TL0741CP IC units.

The sample and hold (S/H) signal was derived from the timing circuit. The sampling signal was fed to the S/H unit of each channel, resulting in simultaneous sampling of the signals. The S/H period was 8 ms (i.e. 1/125 s). The LF398 S/H devices used are of ultra-high DC accuracy with fast signal acquisition time and low droop rate.

An analogue multiplexer was used after S/H so that only one programmable gain amplifier (PGA), A/D convertor and window detector (WD) was necessary. The multiplexing rate was 1000 (i.e. 8 × 125).

A commercially available A/D board from the DT2801 series (DT2805 model)[22] was used to further amplify and digitise the data. The board had a PGA and a 12 bit A/D convertor. The analogue-to-digital conversion time was 25 μs and therefore it was sufficiently fast for the required sampling rate of 125 Hz which corresponded to a multiplexing time of 1 ms. The CNV voltage amplitude could be as low as -5 μV and the PGR amplitude could vary by up to ±2 mV which after being amplified by the fixed voltage gain of 4000 became -20 mV and ±8 V, respectively.

The programmable gain amplifier is situated prior to the A/D convertor and provides a variable gain. Its gain could be software adjusted to either 1, 10, 100 or 500. The particular gain selected was determined by reading the window detector (WD) output. The WD consisted of a series of comparators. The output of these comparators would vary in accordance with the input signal amplitudes. With this arrangement, after issuing the S/H signal, a multiplexer channel was activated, the signal amplitude range was determined by reading the WD output, the PGA gain was adjusted to a suitable value and then the signal was digitised. This was repeated for the eight channels. Each digitisation produced three bytes, two bytes from the A/D convertor output and one from the WD. The WD output was stored together with the corresponding digitised amplitude so that during the data processing the particular gain utilised was known and could be taken into account. The interfacing of the WD and multiplexer

to the PC was realised by a programmable peripheral interface device, PPI (type INTEL 8255A).[23]

An acoustic stimuli generator was required for CNV elecitation. It produced a click by connecting a power amplifier (type TBA820 linked to a loudspeaker) to a DC voltage via an analogue switch (type HFE4016b) for about 20 ms. Then a tone of 1 kHz with 5 s duration was generated by a sine wave generator and also amplified by the power amplifier. A pushbutton attached to the tone generator by a cable allowed the tone to be terminated. An error signal which indicated whether the CNV response was faulty (i.e. pushbutton pressed before the onset of the tone) was obtained through a latch attached to the pushbutton.

The timing circuit provided the necessary S/H signal, measured the intertrial interval and the subject's reaction time. It consisted of two programmable interval timers (Intel 8254) which were added to the PC. Each programmable interval timer (PIT) contained three individually programmable counters. These counters were programmed to generate the necessary signals or to measure the required times. The PC contained a programmable timer, but this could not be used as it was utilised by the PC itself.

Memory requirements

The data recording was carried out at a sampling rate of 125 Hz and with a trial length of 12 s. The experiment was repeated 32 times for every subject, thus recording 32 trials. Eight channels of data were recorded. The PC hard disc could hold the data recordings from 17 subjects. For further recordings the contents of the hard disc were backed up on a magnetic tape by using a Sysgen tape streamer.

Data-recording software

Fig. 6 shows the flow chart of the data-recording software. The programs were written in Turbo-Pascal and 80286 assembly language. Turbo-Pascal was used to enter the data related to recording, for example, the name of the file in which the data was to be stored, the number of CNV trials and the CNV paradigm (the time for the onset of warning and imperative stimuli, and the duration of each trial). The assembly language program was declared as external in the Turbo-Pascal program and was called by the Turbo-Pascal program. Assembly language was used to control the experiment, and to acquire and store the data.

CNV preprocessing steps

Prior to analysing the CNV response a certain amount of digital signal preprocessing had to be carried out. The steps followed were:

(i) Mean (DC) level removal

Even though a highpass filter with a cut-off frequency of 0·0159 Hz was implemented for each channel and various precautions were taken during the data recording and the development stages to minimise any DC offsets (e.g. the use of output offsetting for the instrumentation

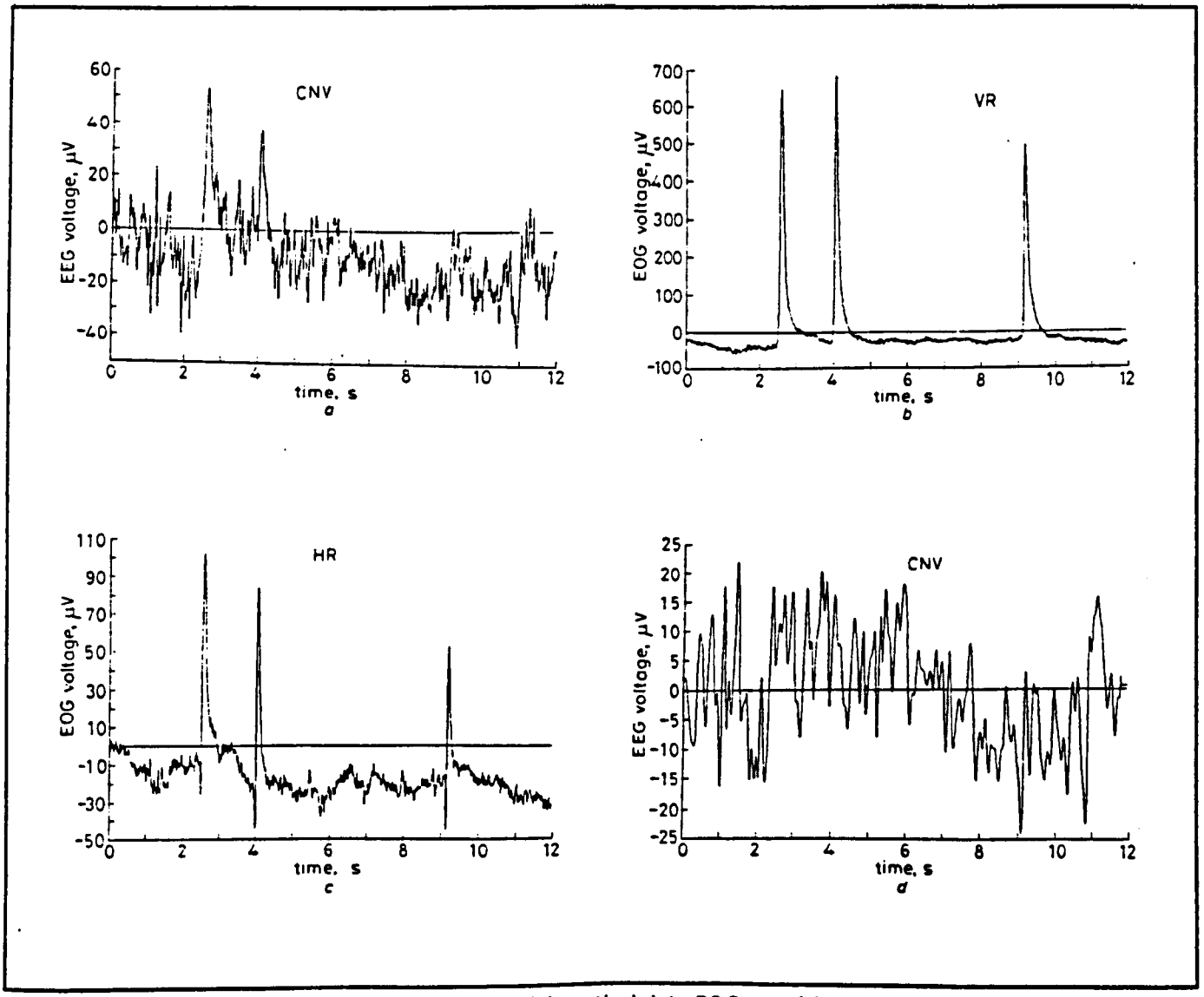


Fig. 7 (*a*) A single CNV trial prior to preprocessing; (*b*) A vertical right EOG plot; (*c*) A horizontal right EOG plot; and (*d*) The single CNV trial of (*a*) after preprocessing

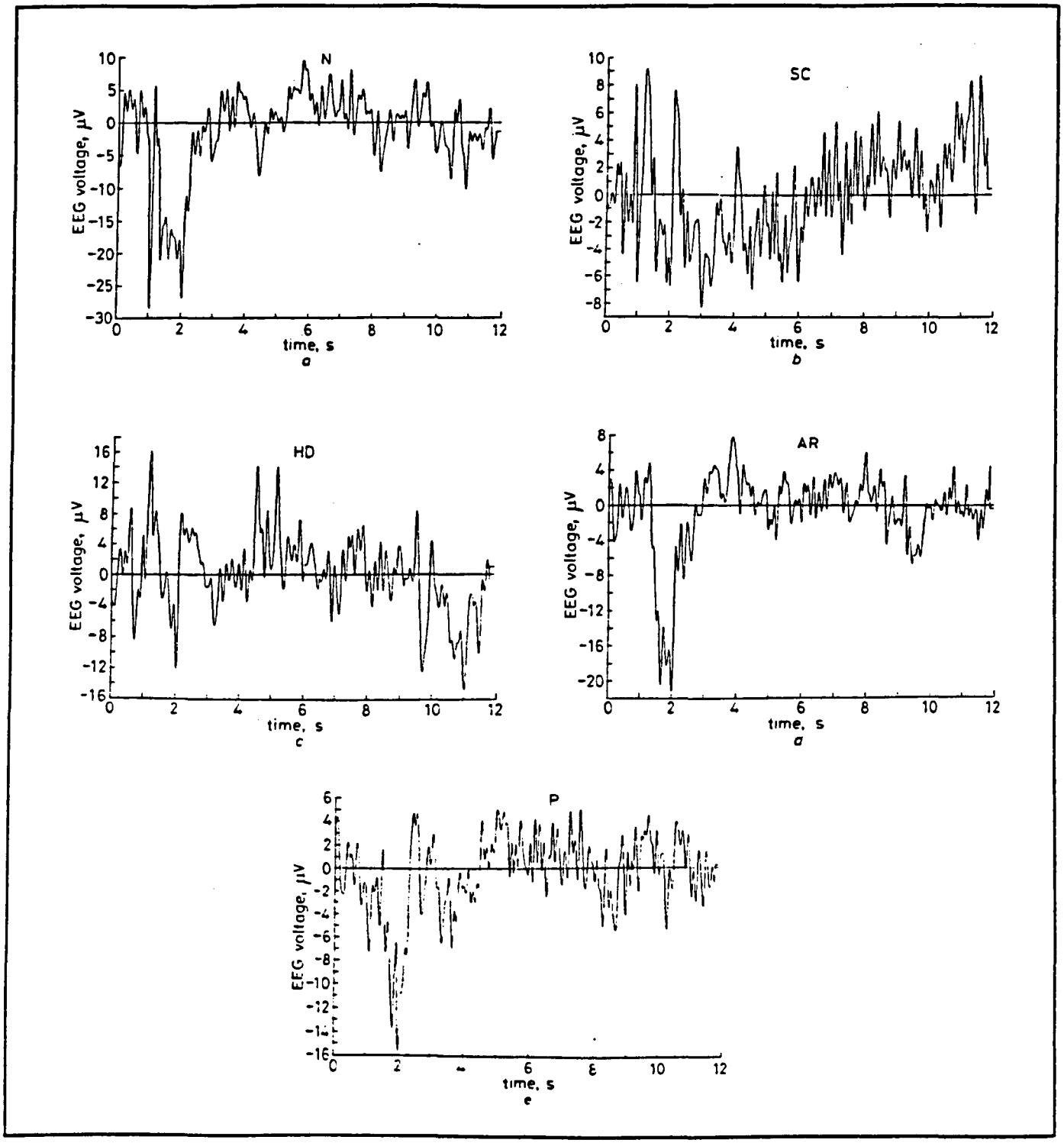


Fig. 8 Typical averaged preprocessed CNV waveform from: (*a*) A normal subject; (*b*) A schizophrenic: (*c*) A Huntington's disease subject; (*d*) An at risk of Huntington's disease subject; and (*e*) A Parkinson's disease subject

amplifiers, as described in Reference 19, and the careful selection of the components), they could not be totally eliminated. Their effects were to cause a shifted baseline. It was desirable to have a baseline reference of zero so that comparison over time could be made and to ensure that the ocular artefact removal algorithm functioned properly. As the CNV trial length was fixed this offset was removed by:

$$X_{kr} = X_k - \frac{1}{N}\sum_{i=1}^{N} X_i \text{ for } 1 \le k \le N \quad (1)$$

where X_k = k^{th} data point,
N = total number of samples per CNV trial,
and X_{kr} = k^{th} data point with the mean removed.

(ii) Baseline correction

A side effect of mean level removal for the CNV responses which had a marked negative shift was to cause a positive shift of the pre- and post-stimulus baseline. Thus it was necessary to re-establish the true baseline. This was achieved by subtracting the mean signal level (Y_{S1}), calculated over that section of the data prior to S1, from the pre-stimulus section:

$$Y_{S1} = \frac{1}{P1}\sum_{i=1}^{P1} X_i \text{ for } 1 \le k \le P1 \quad (2)$$

where $P1$ = the sample number corresponding to the instant of S1,
X_i = the i^{th} data point.

Further, to allow for any small drift during the acquisition of the data, the mean signal level Y_{S2} was also calculated for that section of the data from a point 1 s after S2 (to avoid the auditory evoked potential generated as a result of S2) to the end of the

data record. Y_{S2} was subtracted from this post-stimulus section:

$$Y_{S2} = \frac{1}{(N-P2-D)} \sum_{i=P2+D}^{N} X_i \text{ for } P2 < k \leq N \quad (3)$$

where $P2$ = the sample number corresponding to the instant of S1,
D = the delay after S2 (1 s, or 125 samples),
N = the total number of data points.

Between these two mean values the data was corrected by subtracting the appropriate fraction of the difference, i.e. Y_{Sl}, between these values:

$$Y_{Sl} = \frac{Y_{S2} - Y_{S1}}{P2 - D - P1} (k - P1) + Y_{S1}$$

$$\text{for } P1 < k \leq P2 - D \quad (4)$$

(iii) Digital filtering

A finite impulse response (FIR) lowpass filter with passband and stopband frequencies of 5 Hz and 10 Hz, respectively, was designed. The cutoff frequency of the filter is the arithmetic mean of the bandedges, i.e. 7·5 Hz. The design was based on the FIR filter program given by Rabiner and Gould.[24] A FIR filter was chosen rather than an infinite impulse response (IIR) filter because it does not distort the signal.[25,26] Digital filtering was incorporated to filter out the unwanted high-frequency components in the EEG. The filter length chosen was 29.

(iv) Ocular artefact removal (OAR)

There exist several methods of OAR but the technique applied here was the proportional subtraction technique[27] and is based on the assumption that the measured EEG is a linear combination of the true (uncontaminated) EEG and OA, and that the OA is a linear combination of selected EOGs. The formula used for the OAR procedure was:

$$EEG_c(i) = EEG_m(i) - (\theta_1 HL(i) HR(i) - \theta_2 VR(i) - \theta_3 HL(i) - \theta_4 HR(i))$$
$$\text{for } 1 \leq i \leq N \quad (5)$$

where $EEG_c(i)$ = i^{th} sample value of corrected EEG
$EEG_m(i)$ = i^{th} sample value of measured EEG
$HL(i)$ = i^{th} sample value of horizontal left EOG
$HR(i)$ = i^{th} sample value of horizontal right EOG
$VR(i)$ = i^{th} sample value of vertical right EOG
N = number of data points
and θ = transmission coefficient.

The values of θ were determined by the correlation technique[28] using a non-recursive algorithm. Experiments indicated that the non-recursive method of estimation of θ was superior to that of the recursive technique as the latter may distort the signal.[27]

Waveforms description

The plots of a single CNV trial (prior to preprocessing) and the corresponding vertical right and horizontal right electrooculograms are shown in Figs. 7(*a*), (*b*) and (*c*). The vertical and horizontal left EOG plots are not shown as they were similar to those of the right. The spike-like waveforms at times t = 2·5, 4 and 9 s in the EOG plots are due to eye blinks. These ocular artefacts and the background EEG have contaminated and obscured the single CNV trial of Fig. 7(*a*). It can be seen that the effect of these artefacts is considerably reduced in the preprocessed single CNV trial of Fig. 7(*d*) and now the CNV can be seen between the two stimuli (i.e. S1 and S2 or time intervals 1 and 2 s). As mentioned before, the onset of the stimuli S1 and S2 generates auditory-evoked potentials. These can be seen at time t = 1 and 2 s.

Typical plots of preprocessed averaged (over eight trials) CNV waveforms of a normal subject, a schizophrenic, a Huntington's disease subject, an at risk of Huntington's disease subject, and a Parkinson's disease subject are shown in Figs. 8(*a*)–(*e*). The averaging was necessary to reduce the effect of background EEG on the CNV. This reduction is proportional to the square root of the number of CNV trials used.[29]

Generation of diagnosis results

For every patient considered, data were recorded from an age and sex matched normal control subject. This was done so that comparison could be made between the CNV waveforms of the patients and normal subjects. The patients and their matched normal control subjects were divided into two equal groups in such a way that each group contained roughly similar patients and normal control subjects from the point of view of numbers, age and sex. 20 features (attributes) were selected from the average of eight trials of the preprocessed inter-stimulus interval sections of the CNV waveform from each subject. The features from the first group were used to drive the diagnosis rule (these features were used in training mode) and then the features from the second group (these features were used in the test mode) together with the diagnosis rule were used to test the effectiveness of the technique.

Of several methods (such as discriminant analysis, predictive statistical diagnoses) which are being used by us to obtain the diagnosis results, the artificial neural network (ANN) technique will be described here. ANN has been successfully used in many fields, such as pattern recognition. The reader may refer to Reference 30 for an introduction to ANN, and for more details, to the proceedings of the first IEE international conference on artificial neural networks.[31] ANN comprises programmable neural units. Feature vectors form the input to these units. The structure of the ANN used is shown in Fig. 9. It contains an input, an output and hidden layers. The method used to train the network was based on the back-propagation algorithm. This is a generalisation of the least-mean-squares technique which uses a gradient search method to minimise a cost function equal to the mean square error between the desired and actual outputs of the network.

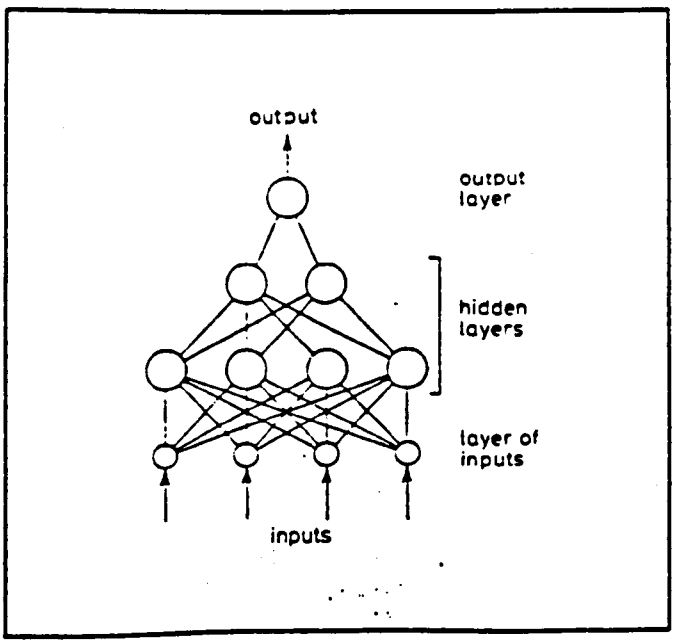


Fig. 9 Artificial neural network used to obtain the diagnosis results

Table 1 The diagnosis success rate obtained for schizophrenia by applying CNV to ANN

Network* structure	Training mode	Test mode
4, 8, 1	100%	92·9%
8, 8, 1	100%	85·7%
16, 8, 1	100%	85·7%
16, 16, 1	100%	85·7%
20, 16, 1	100%	85·7%

*Numbers under this column represent the number of units in input, hidden and output layers, respectively.

The results obtained when the above method was used to diagnose schizophrenia are shown in Table 1. These results are based on the recordings from 14 schizophrenics and their 14 matched normal control subjects. It can be observed that the success rate in the training mode for all the different ANN structures was 100%. In the test mode, however, the best result was obtained when the number of units in the input, hidden and output layers were 4, 8 and 1 respectively. The diagnosis results from Huntington's disease and Parkinson's disease are not included as sufficient data were not available at the time of writing this article.

Conclusion

An integrated system set up around a PC to diagnose brain-related disorders has been developed. The system meets the necessary specifications and when compared to the commercially available systems was cheaper and superior. It is now being applied successfully to the clinical diagnosis of patients.

Acknowledgments

The authors gratefully acknowledge the provision of normal and patient category subjects, the help and continuing support of the staff from the Department of Neurological Sciences, Plymouth general hospital, especially Dr. E. M. Allen, Mr. N. R. Hudson, and S. Oke. They are also grateful to all the subjects who participated in the data recordings.

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6. Application of artificial neural networks to the identification of schizophrenic patients based on the contingent negative variation.

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There have been consistent reports describing abnormalities such as the reduction in the amplitude of the contingent negative variation (CNV) responses of schizophrenic patients and the presence of a post-imperative negative variation. Artificial neural networks which are computer models that simulate the functioning of the brain in a very simplified manner have been used successfully in many pattern recognition problems. We have applied them to the identification of schizophrenic patients based on the contingent negative variation.

The CNV responses of 20 schizophrenic patients and 20 age/sex matched normal control subjects were preprocessed and averaged (over 8 trials). Twenty time domain features were selected from each averaged preprocessed CNV response. The CNV features of half the patients and their matched normal control subjects were used to train the neural network. The CNV responses of the remaining patients and their normal control subjects were used to test the effectiveness of the neural network in the test mode.

The performance of the neural network in identifying the CNV responses of the schizophrenic patients in the training and the test mode was 100% and 90% respectively. This result indicates that neural networks are a valuable tool for the identification of schizophrenic patients.

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The Application of Unsupervised Artificial Neural Networks to the Sub-classification of Subjects At-risk of Huntington's Disease

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Summary

The Contingent Negative Variation (CNV), which is an evoked response in the human electroencephalogram (EEG), was measured for a number of Huntington's Disease patients (HDs) and subjects at-risk of developing HD (ARs), and for equal numbers of matched normal subjects. The sampled voltage response values and the duration of the CNV were then used as input data to Kohonen and ART2 unsupervised artificial neural networks to classify the subjects. The two methods gave similar results for the HDs vs normals which also agreed with the results of a cluster analysis. The results of attempting to identify abnormal ARs showed that the ART2 results showed partial agreement with the results of the Kohonen network and cluster analysis. The application of these unsupervised neural networks to the sub-typing of clinical categories appears to offer a relatively simple tool suitable for hardware implementation.

Introduction

It is of clinical importance to be able to identify, monitor, and pre-symptomatically diagnose the genetically inherited and fatal brain disease known as Huntington's Disease. The Sheffield/Plymouth group have succeeded in differentiating HD patients from normals using the Contingent Negative Variation (CNV) which is an evoked response potential (ERP) in the electroencephalogram (EEG) and which is modified by the disease .The CNV was recorded using purpose-designed instrumentation (1). In the first method (2) the CNV was transformed into its Fourier harmonic components and then these were analysed statistically. This complicated approach was then replaced by pattern recognition in the time domain which was much simpler (3). Voltage samples of the CNV waveform were pre-processed and then used together with the duration of the CNV as inputs to an artificial neural network, the output of which after supervised training classified the subject as HD or normal. Attempts were then made to identify abnormal ARs ie ARs whose CNVs were abnormal, and who therefore might be in the early stages of HD. Because there was no means of knowing whose CNVs were abnormal it was necessary to identify techniques designed to form classes based upon unclassified data. This was done using Ward's cluster analysis method which identified some abnormal ARs based upon the time domain data (4). It was then of interest to establish whether similar results could be obtained more easily using unsupervised neural networks. It would then be possible to provide a software package for the detection of abnormal ARs which would be simple to use, or to develop a hardware version available as a black box of electronics. There were two competing artificial neural networks which might be suitable for the task, namely the Kohonen network (5) or the ART (Adaptive Resonance Theory) networks (6,7). Both possess the crucial ability to learn (be trained) in the unsupervised mode. However they work differently and have different output formats. The Kohonen network responds to input data by producing an output map in which each input data set produces a characteristic pattern which depends upon the class to which it belongs. Recognition of the pattern identifies the class. By comparison the ART networks have one output node specifically assigned to each of the possible patterns. Activation of a node identifies the class. The Kohonen network is provided with all the data and forms the characteristic patterns from it. The ART networks classify the data as it becomes available. Earlier classes are retained in memory and new classes are identified and assigned to unused output

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nodes. Both methods have been applied to the identification of abnormal ARS and the results compared with those of the cluster analysis. This is the topic of this paper.

CNV acquisition

11 HD patients, 21 ARs, and their age and sex matched normal control subjects were enrolled for this study. The CNV was recorded from the convexity of the scalp (vertex) using linked earlobes as the reference. Electro-oculograms (EOGs) were also recorded for use in the removal of contaminating ocular artifacts. The data recording system has been described elsewhere (1) as has the CNV (1). Figures 1 and 2 show the individual CNV waveforms of a normal subject and an HD patient respectively. The HDs were numbered 1 to 11 and their matched normals 12 to 22. The ARS were numbered 1 to 21 and their matched normals 12 to 22.

CNV Pre-processing

CNV pre-processing was necessary to reduce the effects of background EEG and ocular artifact contamination. This involved applying the following routines to each individual CNV response: mean level correction, baseline correction, digital low-pass filtering (cut-off 7.5 Hz), and ocular artifact removal. The average of eight CNV trials per subject was then taken to reduce the effect of the background EEG. Figures 3, 4, and 5 show the pre-processed and averaged CNV responses of a normal subject, an HD, and an AR respectively. The procedures are described in detail in (1).

Feature extraction

After pre-processing, features were extracted from the averaged CNV waveforms. 16 amplitude measures were obtained from the 64 data points immediately prior to the imperative stimulus (S2). Every four consecutive voltage samples was averaged to produce 16 features. The seventeenth feature was the time difference between S2 and the point where the CNV trend returned to its original baseline. These features were the data used in each method.

Kohonen method

The algorithmic version of the Kohonen self-organising map (5) given in (8) was used. The aim is to map exemplar class patterns of input data on to the weights connecting the inputs to the corresponding region of output nodes which is associated with the particular class. In this way data belonging to a particular class will always activate the same region of the output map. Thus when the network is fed unclassified data the classes become revealed by the patterns formed in the output map.

The winning output node was identified as the one associated with the smallest Euclidean distance between the input data and its weights. In the weight up-dating procedure all nodes in the neighbourhood of the winning node had their weight vectors adjusted incrementally to become nearer to the input data vector. The winning node was placed in the centre of the neighbourhood which was shrunk as the training progressed.

Patterns of activity within the network and output patterns were more readily identified by displaying the activity of each node. The activity is the inverse of the Euclidean distance associated with a node. The activity values were scaled within the range 0 to 1 using the arctan function. Otherwise winning nodes with near zero distances would result in infinite activity.

There were 17 inputs corresponding to the 17 input features. The output map contained 10 x 10 nodes. The initial weights were random numbers between 0 and 1, and the input data was normalised to lie between 0 and 1. The gain term which controls the amount by which the weight vectors were adjusted was reduced from 0.2 during training in steps of 0.00001 every two cycles during neighbourhood sizes of 3 or 2, and by 0.00001 every 100 cycles when the neighbourhood size was 1. The initial neighbourhood size was 3 being reduced by 1 every 20,000 cycles down to 0. 100,000 training cycles were used. To assist the pattern identification an activity threshold was set. If this was exceeded the node was on and was illuminated on the screen, otherwise it was off and not illuminated.

With a 486 PC (25 MHz) having an on-board floating point calculation unit the average training time was approximately 30 minutes.

ART method

The adaptive resonance theory, or ART, neural networks, based on the models of Grossberg and Carpenter, are recommended for the real-time unsupervised grouping of patterns, as they are encountered in an arbitrary "environment". There is no separation of activity into training and recognition phases and, while learned pattern templates are stable, the network retains plasticity ie it can form a new template at any time a novel pattern appears, though if the input is close enough (as defined by an adjustable number, vigilance) to a known group, it joins it and modifies the template. Thus vigilance controls the partitioning of the patterns with lower vigilance forming coarser categories. At first, recognition of known patterns may require a search of several candidate templates before the matching one is found, but after a few repetitions of a fixed (even a long) sequence, the network stabilises and known patterns are immediately classified without search.

The speed and self-organisation of ART networks make them attractive as tools for the classification of subjects by multivariate data.

Each pattern of the 17 data is read into a sufficiently wide input array of "nodes" in layer F1 (figure 6), where it may be processed (ART 2). From F1, it activates F2 via "bottom-up" connections, which are initialised with small random weights. The F2 node with maximum activity "wins" and all others are suppressed. In parallel implementation this would be done by competitive inhibition between F2 nodes. The winning signal is filtered via the "top-down" weights, back to F1, where the emerging vector is compared with the input pattern. A similarity ratio exceeding vigilance is rewarded by learning and resonance. In learning the outstar and instar weights between the winner and F1 are modified to reinforce the selection of the winner and improve the match. In resonance the F2 winner stays active with this input and represents its cluster. Thus, the outstar weights from the winner constitute the template pattern for this cluster. On the other hand, mismatches inhibit winners while the search cycle continues. If no existing cluster fits, an unused F2 node will eventually win and start a new cluster. Only the size of F2 limits the number of clusters that can be formed. After all the patterns have been cycled a few times, the clusters stabilise.

ART 1

The ART 1 network (6) accepts only patterns of binary numbers, but as it is the simplest ART to compute, an attempt was made to apply it. ART 1 is also much better-defined than later models, and the conditions for its stability are rigorously proved in the literature. The real numbers were first converted to histogram-like patterns of bits. Thus, if 10 bits were used and the data scaled between 0 and 1, 0.7 became 7 1's followed by 3 0's, and 170 input nodes were needed for the whole pattern. The limit was 15 bits, so the resolution was crude. In ART 1, top-down weights are binary, and the template is compared with the input by ANDing, then dividing the number of 1's remaining by the number in the input. The learning is "fast" ie the top-down outstar changes in one step to match the ANDed vector, and the bottom-up instar becomes parallel to this vector, but scaled to allow sparse templates to win when inputs match them.

ART 2

In ART 2 (7), F1 is modified for real number inputs, which are first contrast-enhanced and normalised by F0. Competition among F1 nodes is introduced, to enhance peaks and suppress low activity as noise. In the computer algorithm, this is simulated by creating "nodelets" within each F1 node, which successively suppress low signals and normalise the remaining patterns. Two cycles are seen in each node (figure 7) and the pattern matching occurs at their interface. The resulting vector at U is compared with the outstar template at P, to reset F2 or refine the weights as in ART1.
Here, ANDing of vectors is replaced by measuring the length of a vector made by normalised linear combination. Learning can be slow, where a new weight is a linear combination of the old weight and the activity at P, or fast, as in ART 1. In all, there are 7 parameters to adjust: learning rate, vigilance, top-down filter gain, two feedback gains and noise threshold in F1, and a constant used in vector comparison. Some of these have

stability constraints, but ART 2 is clearly more complex to use than ART 1, while having greater versatility.

The algorithm first tested in the Sheffield group, ART 2A, was based on a simplification of the full ART 2 model, which was proved (9) to have equivalent dynamics to ART 2 when it is restricted to fast or intermediate modes of learning. ART 2A is recommended for real-time applications, but even slow learning in ART 2 is fast compared to most neural network simulations. In intermediate learning, free nodes undergo fast learning, while those committed to a cluster learn slowly. In ART 2A, F1 and the reset mechanism are much simpler (the latter reduces to a measure of the angle between input and template).

Results

The results of using the two unsupervised networks and the cluster analysis are compared in Tables 1 and 2. Table 1 refers to distinguishing between the known classes of HDs and matched normals, while Table 2 refers to the classification of ARs and their matched normals. It can be seen from Table 2 that some ARs have been classed as abnormal, which was the desired result. Some of the ARs have been classified as abnormal by more than one method. This suggests that those subjects could be in the early stages of HD.

With all the ART networks, test patterns of real numbers in clearly discernible clusters were successfully, and very rapidly, grouped, and noise within a variable was rejected, using a wide range of network parameters. However, for the noisy EEG data, the clusters revealed were sensitive to the parameters. The HD data was used to 'tune' the networks, with the aim of minimising the number of badly classified subjects. Then the AR data were investigated. ART 1 managed to classify the invented test patterns, but was inadequate for the EEG data. ART 2A was capable of being fairly well tuned to HD data, but then made little sense of AR data, confirming the view that ART 2 needs slow learning with noisy data. The full ART 2 model was therefore used.

Two different ways of controlling the formation of new categories for novel inputs have been tried based on the vigilance parameter. Vigilance prevents the inclusion of a mismatched pattern in a cluster, by withdrawing that cluster from competition, allowing free F2 nodes to "win". In the absence of reset (zero vigilance), the size of initial bottom-up weights can be used to affect the stability of established clusters. As these approach their upper limit, free nodes are more likely to beat the poorly matched committed nodes, though they will lose to well matched ones. While the Cretan group have used a zero-vigilance model (ZV), in which a noise threshold and initial weights were manipulated, the Sheffield network was tuned mainly by varying vigilance and a continuous sigmoid version of the noise threshold. Both models were tried for ART 2A, and results for HC data are tabulated.

HC results show a fair correlation with those from cluster analysis, especially ART 2 with ZV. Of course, HC was used to tune the network, but this should not be confused with training of a supervised network, where the categories are first created with known exemplars taken from a population homogeneous with the test data. Thus, there are not enough degrees of freedom to force ART 2 to correlate inputs with arbitrary outputs. The AR results are more divergent, though both AR and HC controls are correctly identified by all ART 2 models, 100 % in ZV and with one error in the others. The AR results with ZV match cluster analysis quite well.

It can be seen that there is very good agreement between the cluster analysis and Kohonen results. At present it is not clear whether this is because the two methods share an underlying principle or whether these methods are robust compared to ART 2. Certainly the results indicate that ART 2 is sensitive to the chosen parameters. It is also debatable that, because the Sheffield ART 2(b) network identified some additional abnormals as well as the same abnormals as the Kohonen and cluster methods, whether it is a more sensitive detector of abnormals or whether it is unreliable. This query may be solved by more analysis, otherwise it will be necessary to wait until the abnormal ARs have had sufficient time to develop symptoms - and that will take years.

An interesting suggestion has been made by Burke (10) that ART 2 is formally equivalent to a K-means cluster analysis, and even shares characteristics with the cruder single leader algorithm variant. The latter is refuted by Carpenter, Grossberg and Rosen (9).

Conclusion

All four methods have shown promise in the pre-symptomatic detection of HD in ARs. Further investigation will be necessary to determine which of the unsupervised networks is the more reliable. It will then be worthwhile implementing it as either a software system and/or as hardware for clinical practice.

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TABLE 1: RESULTS FOR HDs AND MATCHED NORMALS

SUBJECT NUMBER	SUBJECT CLASS BY NUMBER						
	ART 2 SHEFFIELD NORMALISED		ART 2 CRETE NORMALISED	ART 2A SHEFFIELD NORMALISED		KOHONEN NORMALISED	CLUSTER ANALYSIS
	(a)	(b)		(a)	(b)		
HD1	3	3	3	2	3	HD	C1
HD2	3	3	3	2	3	HD	C1
HD3	3	3	3	2	3	HD	C1
HD4	3	3	3	2	4	HD	C3
HD5	3	1*	3	2	3	HD	C3
HD6	2	2	2	2	5	HD	C1
HD7	2	2	1*	1*	2	HD	C1
HD8	1*	1*	3	2	1*	HD	C1
HD9	3	3	3	2	3	HD	C3
HD10	3	3	3	2	3	HD	C3
HD11	1*	2	1*	1*	1*	HD	C1
N12	1	1	1	1	1	N	C2
N13	3*	1	1	2*	3*	N	C2
N14	1	1	1	1	1	N	C2
N15	1	1	1	1	1	N	C2
N16	1	1	1	1	1	N	C2
N17	1	1	1	2*	1	N	C2
N18	1	1	1	1	1	N	C1*
N19	1	1	1	1	1	N	C2
N20	1	1	1	1	1	N	C2
N21	1	1	1	1	1	N	C2
N22	1	1	1	1	1	N	C2

* *denotes incorrect classification*

ART PARAMETERS

	A		B		C		D		ℓ		Θ		ß	
	(a)	(b)	(a)	(b)	(a)	(b)	(a)	(b)	(a)	(b)	(a)	(b)	(a)	(b)
SHEFFIELD ART2A	-	-	-	-	-	-	-	-	0	0.7	0.24	0.23	0.1	0.05
SHEFFIELD ART2	0.7	0.7	0.7	0.7	0.2	0.2	0.8	0.8	0.95	0.97	0.24	0.24	0.5	0.03
CRETE ART2	10		10		0.1		0.9		0		0.0727		0.235	

TABLE 2: RESULTS FOR ARs AND MATCHED NORMALS

SUBJECT NUMBER	SUBJECT CLASS BY NUMBER				
	ART 2 SHEFFIELD		ART 2 CRETE	KOHONEN	CLUSTER ANALYSIS
	(a)	(b)			
AR1	1	2+	1	N	C1
AR2	1	1	1	N	C2
AR3	2+	1	1	N	C1
AR4	1	2+	2+	+	C3+
AR5	2+	2+	1	+	C3+
AR6	1	2+	1	N	C4
AR7	1	1	1	N	C4
AR8	1	1	1	N	C4
AR9	1	2+	2+	+	C3+
AR10	1	2+	1	N	C4
AR11	1	2+	2+	+	C3+
AR12	2+	2+	2+	+	C3+
AR13	1	1	1	N	C4
AR14	1	1	1	N	C1
AR15	1	2+	1	N	C2
AR16	1	2+	2+	+	C4
AR17	2+	2+	2+	N	C4
AR18	2+	2+	1	N	C1
AR19	1	2+	1	+	C3+
AR20	2+	2+	1	+	C3+
AR21	1	1	1	N	C2
N22	1	1	1	N	C1
N23	2+	3+	1	N	C2
N24	1	1	1	N	C2
N25	1	1	1	N	C1
N26	1	1	1	N	C4
N27	1	1	1	N	C2
N28	1	1	1	N	C4
N29	1	1	1	N	C4
N30	1	1	1	N	C1
N31	1	1	1	N	C1
N32	1	1	1	N	C2
N33	1	1	1	N	C4
N34	1	1	1	N	C1
N35	1	1	1	N	C4
N36	1	1	1	N	C4
N37	1	1	1	N	C2
N38	1	1	1	N	C2
N39	1	1	1	N	C4
N40	1	1	1	N	C2
N41	1	1	1	N	C4
N42	1	1	1	N	C1

\+ *denotes identified as abnormal*

ART PARAMETERS

	A		B		C		D		ρ		Θ		ß	
	(a)	(b)	(a)	(b)	(a)	(b)	(a)	(b)	(a)	(b)	(a)	(b)	(a)	(b)
SHEFFIELD ART2	1	1	1	1	0.2	0.2	0.8	0.8	0.985	0.99	0.23	0.20	0.03	0.03
CRETE ART2	10		10		0.1		0.9		0		0.0727		0.235	

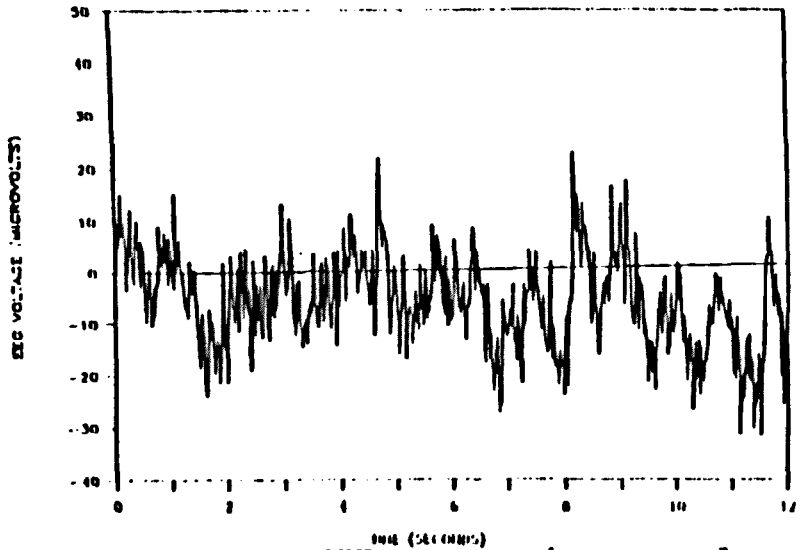


Fig. 1 The CNV response in a normal subject.

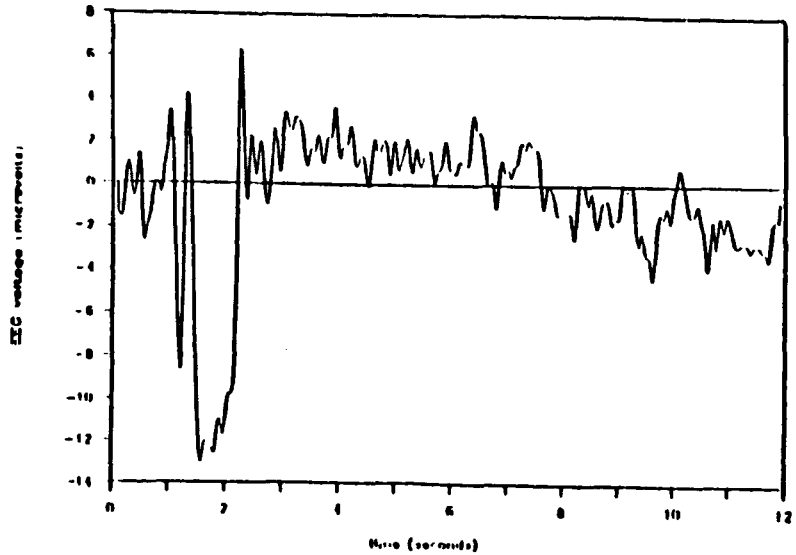


Fig. 3 The preprocessed CNV response in a normal subject.

Fig. 2 The CNV response in a Huntington's disease subject.

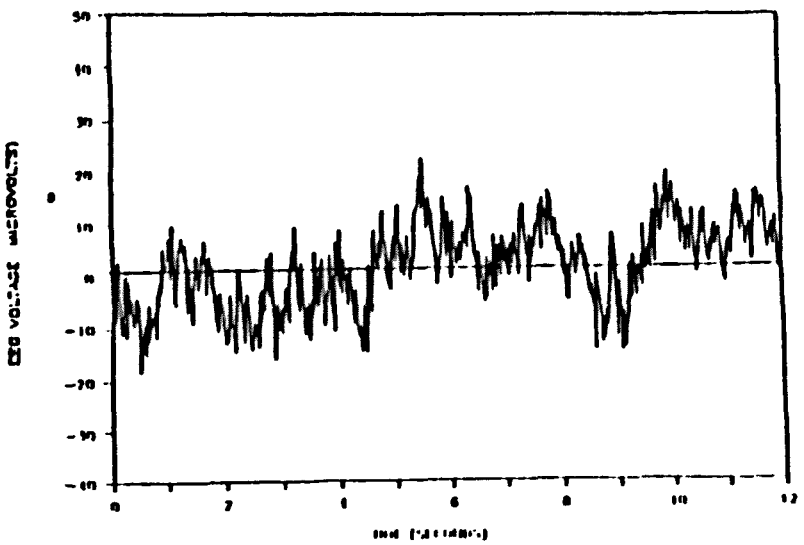


Fig. 4 The preprocessed CNV response in a Huntington's disease subject.

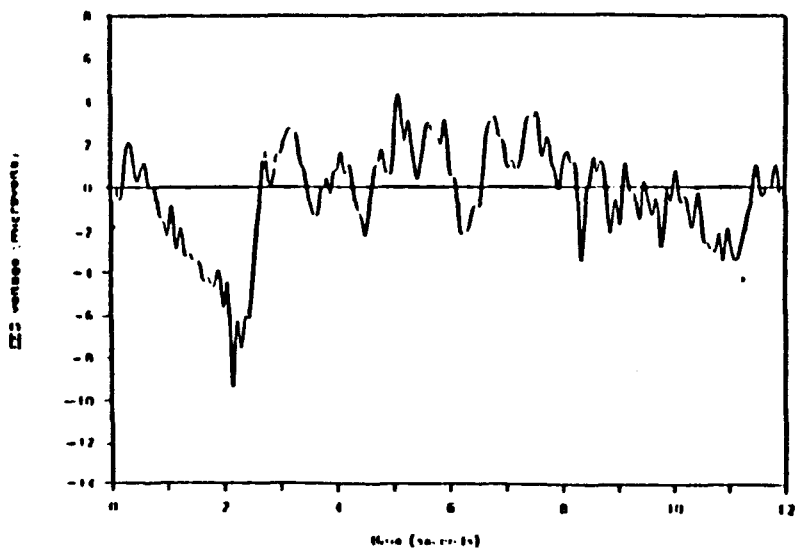


Fig. 5 The preprocessed CNV response in an at risk of Huntington's subject.

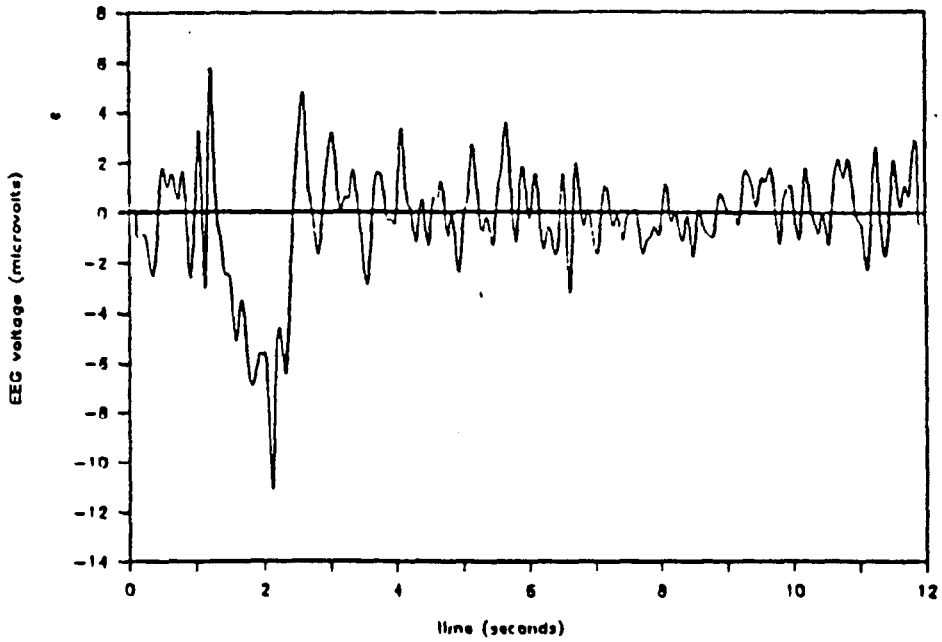


Fig. 6 ART1 network.

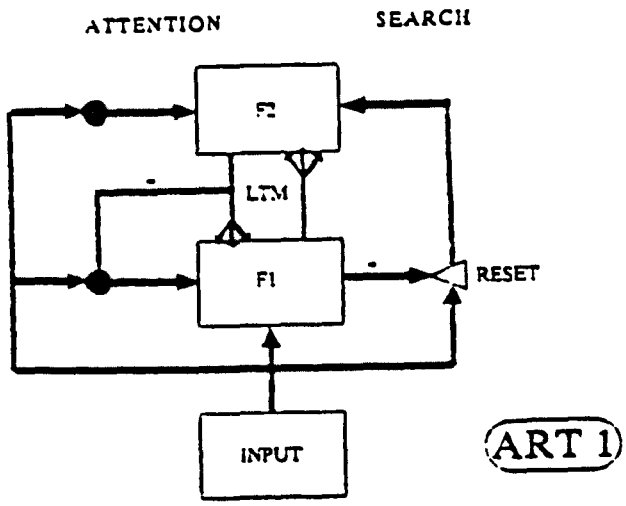
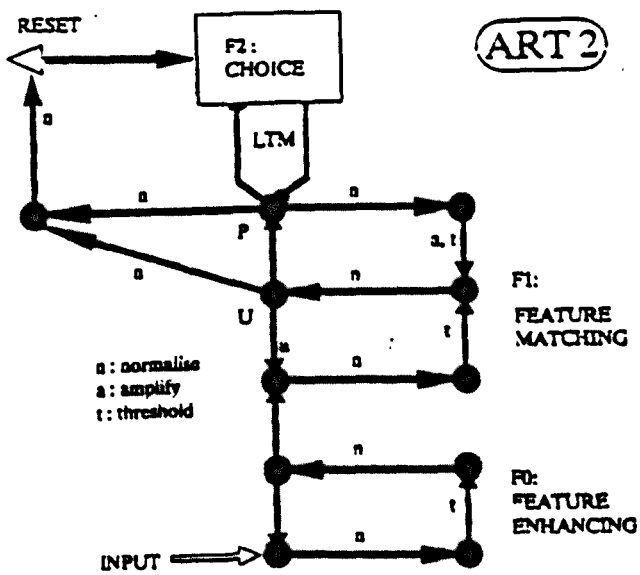


Fig. 7 ART2 network.



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A Pilot Study of the Computerised Differentiation of Huntington's Disease, Schizophrenic, and Parkinson's Disease Patients Using the Contingent Negative Variation

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Abstract

In this study a potential known as the contingent negative variation was used to differentiate between schizophrenic, Parkinson's disease (PD), Huntington's disease (HD) patients and normal control subjects. The aim was to assist diagnosis and the avoidance of false-diagnosis. 20 schizophrenic, 16 PD, 11 HD, and 43 normal control subjects were enrolled for this study. The discriminatory variables were generated by applying spectral analysis to pre- and post-stimulus sections of the CNV responses. The patient differentiation was achieved by using the measured variables in a discriminant analysis program. It was possible to accurately differentiate between HD, schizophrenic, PD patients and normal control subjects.

It was also attempted to differentiate between HD and schizophrenic patients, HD and PD patients, and schizophrenic and PD patients. The test results indicated that the method is useful in differentiating between these patients.

This study had a number of limitations. It was based on a limited number of individuals, and an analysis of medication effects on the test results and the test-retest reliability assessment could not be carried out.

Keywords: Huntington's disease, schizophrenia, Parkinson's disease, contingent negative variation, patient differentiation, spectral analysis, EEG processing, discriminant analysis.

1 Introduction

The aim of this study was to develop a computerised method of differentiating between schizophrenic, Parkinson's disease (PD), and Huntington's disease (HD) patients and normal subjects using the contingent negative variation (CNV) which would assist diagnosis and help to avoid false diagnosis.

HD is a fatal and progressive neurodegenerative disease which places 50% of the off-spring of the HD patients 'at risk' (AR) of developing the disease (Hayden, 1981). Its symptoms usually appear in the third to fifth decade and include involuntary movements and intellectual deterioration commonly accompanied by psychiatric symptoms. The disease is inherited through a defective gene localised to the short arm of chromosome 4 (Gusella et al., 1983). Studies using computed tomography (CT) and positron emission tomography (PET) showed neuropathological changes in several parts of the brains of HD patients. The affected areas include frontal cortex (Goldman-Rakic, 1987; Hayden, 1981; Adams et al., 1984), but the brunt of the changes (typically severe neuronal loss) are in the striatum (Mazziotta, 1989). The striatum is part of the basal ganglia and is referred to two masses of nuclei called the caudate nucleus and putamen. There is no single definitive test for diagnosing HD, therefore its diagnosis has been based on: i) A positive family history (ie. when the patient has an affected parent), ii) observation of choreic movements and psychiatric disturbances and iii) detection of relevant brain structural abnormalities using PET and CT scans. A genetic presymptomatic test for the individuals AR of HD is possible but it excludes some of the AR patients because the marker used in the test does not detect the gene itself and therefore testing is only possible if suitable family members are available, so that the affected chromosome can be identified (Mirsa, et

al., 1988; Harper et al., 1988; Jackson, 1987).

Schizophrenia is an illness with symptoms such as hallucinations, delusions and thought disorder. Several structural brain abnormalities were observed in schizophrenic patients (Ron and Harvey, 1990). The commonest were enlargement of the lateral and third ventricles and cortical atrophy (Revely, 1985; Weinberger et al., 1983). There has also been evidence of a reduction in volume of the hippocampus in schizophrenic patients (Falkai and Bogerts, 1986). Some investigators shoved a distinct relationship between the structural brain abnormalities and the symptoms in patients with schizophrenia. Marks and Luchins (1990) provided a review of some of those reports. The identification of patients with schizophrenia has been based on monitoring the symptoms and observation of the structural brain abnormalities related to the disorder.

Parkinson's disease (PD) was originally described by James Parkinson (Parkinson, 1817). PD is a progressive movement disorder which affects the nervous system. Its main clinical symptoms are: i) Body tremors at rest, the tremor mainly affects a limb or limbs but it may also be observed in other areas such as jaw and lips. ii) Muscle rigidity, this may cause stiffness and muscle discomfort. iii) Slowness of active movements. iv) Postural instability. A number of secondary clinical symptoms such as dementia and depression may also be observed in some PD patients. The cause of PD is unknown. The studies in progress to identify its cause include a search for an environmental toxin (Stern and Hurtig, 1988). PD is characterised pathologically by: i) Degeneration of the dopaminergic neurons from the substantia nigra (Bennett, 1988). The substantia nigra is a small nucleus considered a part of the basal ganglia. ii) The appearance of Lewy bodies in the substantia nigra (Gibb, 1987). There is no

definitive laboratory test for diagnosing PD. Therefore, its diagnosis has been based on a careful study of the patient's medical history and through physical and neurological examination (Vernon, 1989).

An event-related potential (ERP) is the brain electrical activity that occurs in association with an eliciting stimulus. The ERPs have been valuable in the better understanding of the brain cerebral physiology and in patients with known or suspected disorders of brain function (Chiappa, 1990; Picton, 1988). The CNV is an ERP first reported by Walter et al. (1964). It is a negative shift in the EEG potential measured on the scalp and compared to the potential of the electrical reference electrode placed on a suitable site such as earlobe (Tecce and Cattanach, 1987; McCallum, 1988). The CNV elicitation involves the presentation of a warning stimulus S1 (such as a click) to warn the subject of the upcoming imperative stimulus S2 (such as a tone). The subject is asked to respond to the imperative stimulus (eg. by pressing a pushbutton to terminate the tone). A schematic drawing of a CNV waveform is shown in Figure 1. The CNV is considered as having an early potential component which is maximal over the frontal cortex and a readiness potential component which has a more central distribution over the motor areas of the cortex (Rohrbaugh, et al., 1976). The CNV was used in this study because: i) it is considered to be a measure of the brain-behaviour functions (Tecce, 1972), ii) there have been consistent reports of changes in the CNV responses of the patients with any of the above disorders and iii) the dysfunction of the prefrontal cortex has been directly or indirectly implicated in schizophrenia, PD and HD (Goldman-Rakic, 1987). Furthermore, because some of the symptoms (such as intellectual deterioration) in schizophrenia, PD, and HD are common, the differentiation of the patients of one category from another category would be of interest.

A spectral analysis of the CNV response indicated differences between some harmonic frequency components of the HD patients and normal subjects (Jervis et al., 1984; Jervis et al. 1989a). The CNV responses of 29 schizophrenic patients and 52 normal control subjects were analysed by Abraham (1989). He found that it was possible to identify some of the patients. Prolonged CNV has been observed in the majority of schizophrenic patients (Roth, 1977). McCallum et al. (1970) observed a general reduction in the CNV amplitude of PD patients. This was later confirmed by Cohen (1974).

2 Experimental Procedure

The HD, PD and schizophrenic patients were all confirmed cases and were selected by a neurophysiologist (EMA) and a psychiatrist (SO). A record (containing the names and amounts) of the medication taken by the patients was obtained. The normal subjects were selected by EMA and SO making sure that they did not have any disorder which might affect their CNV responses. All subjects were able to co-operate for the experiment.

The severity of the symptoms in schizophrenic patients was measured using the Diagnostic and Statistical Manual of Mental Disorders (DSM III, 1980). Nine symptoms were measured. Each schizophrenic patient was given a score for each measured symptom. The scores varied between 0 (when the symptom was not observed) and 5 (when the symptom was severe). The sum of the scores (SOS) was obtained for each schizophrenic patient. The minimum value of the SOS was 8. This corresponded to a patient who was least affected by the illness. The maximum value of SOS was 29. This corresponded to the patient most affected by schizophrenia. The mean and standard deviation values for the SOS were 18.35 and 6.45 respectively.

The severity of the disease in the HD and PD patients was assessed using a grading scale which varied between 1 and 5. The grades are shown in Table 1. Grade 1 included those newly diagnosed HD and PD patients for whom the disease had not affected their ability to lead a normal life (eg. they could work etc.). Grade 5 included those patients who had severe HD or PD and were totally dependent on others. The severity of the disease in patients classed as grades 2, 3 and 4 fell between grades 1 and 5, ie. those classed as grade 2 needed some assistance to lead a normal life, those classed as grade 3 could not live a normal life but they were self caring and those classed as grade 4 needed significant help.

The data recording system consisted of an IBM personal computer (used to control the experiment, acquire, store, and process the data), an eight channel EEG machine (which provided a hardcopy of the data recording and was used to set the recording montage), a signal conditioning unit (this amplified and filtered the signals), and an acoustic stimulus generator. The system -3dB pass-band was 0.0159Hz to 30Hz. The warning and imperative stimuli were a click (approximately 70dB sound pressure level (SPL)) and a 1kHz tone (approximately 90dB SPL). On hearing the imperative stimulus, the subjects pressed a handheld pushbutton to terminate it. In order to familiarise the subjects with the experiment, 10 presentations were made, initially, with the subjects only listening, then the subjects participated in 15 practice trials. Following that, 32 CNV trials were recorded per subject. The CNV was recorded from the convexity of the scalp using linked earlobes as the reference. Four channels were allocated for electro-oculogram (EOG) recording. The positions of the EOG electrodes are shown in Figure 2. The data were recorded using d.c. silver-silver chloride electrodes. The impedance between any electrode pair was ensured to be less than 5kΩ during the recording. The subjects' reaction times to the

imperative stimulus were also recorded. The sampling rate was 125Hz. The CNV trial duration was 12 seconds, corresponding to 1 second prior to the warning stimulus, a 1 second inter-stimulus interval and 10 seconds post-imperative stimulus recording. The CNV trials were separated by a random interval which varied between 100ms to 400ms. The data recording system automatically rejected the faulty trials (a CNV trial was considered faulty if the subject did not respond correctly to the imperative stimulus). The CNV trials grossly contaminated by ocular artefact (OA) in the sections of interest were also rejected.

3 CNV Data Preprocessing

Preprocessing was necessary in order to reduce the effect of the background EEG and OA. The procedure consisted of: mean level removal, baseline correction, ocular artefact removal, and digital low-pass filtering. A description of the steps follows.

3.1 Mean Level Removal

It was desirable to have a d.c. level reference of zero so that comparison over time could be made and to ensure that the ocular artefact removal algorithm functioned properly. As the CNV trial length was fixed this offset was removed by,

$$X_{kr} = X_k - \frac{1}{N}\sum_{i=1}^{N} X_i \quad \text{for} \quad 1 \le k \le N \qquad \ldots(1)$$

where X_k = k^{th} sample value,
N = total number of samples per CNV waveform,
and X_{kr} = k^{th} sample value with the mean removed.

3.2 Baseline Correction

The mean level removal caused a positive shift of the pre- and post-stimulus baseline. To correct this, it was necessary to carry out a baseline correction. This was achieved by initially subtracting the mean signal level (Y_{S1}), calculated over that section of the data prior to the warning stimulus from the pre-warning stimulus section where,

$$Y_{S1} = \frac{1}{P1} \sum_{i=1}^{P1} X_i \qquad \ldots(2)$$

P1 = the sample number corresponding to the instant of S1,
X_i = the i^{th} sample value.

The mean signal level Y_{S2} was also calculated for the section of the data from a point one second after the imperative stimulus section to the end of the data record. Y_{S2} was subtracted from the corresponding section (ie. P2+D to N),

$$Y_{S2} = \frac{1}{(N-P2-D)} \sum_{i=P2+D}^{N} X_i \qquad \ldots(3)$$

where P2 = the sample number corresponding to the instant of S2,
D = the delay after S2 (1 second, or 125 samples),
N = the total number of samples per CNV waveform.

The section between P1 and P2+D was corrected by subtracting Y_{ISI} which was the appropriate fraction of the difference between Y_{S1} and Y_{S2}, where,

$$Y_{ISI} = \frac{Y_{S2} - Y_{S1}}{P2 + D - P1} (k-P1) + Y_{S1} \quad P1 < k \leq P2+D \qquad \ldots(4)$$

k = the sample number.

3.3 Digital Filtering

Digital low-pass filtering was necessary to filter out the unvanted high frequency components in the EEG. A finite impulse response low-pass filter (FIR) with the cutoff frequency of 30Hz was designed using the computer program given by Rabiner and Gold (1975). A FIR filter was chosen rather than an infinite impulse response (IIR) filter because it does not distort the waveforms.

3.4 Ocular Artefact Removal (OAR)

The technique applied was that of proportional subtraction (Jervis et al., 1989b). This is based on the assumption that the measured EEG is a linear combination of the uncontaminated EEG and the OA, and that the OA is a linear combination of selected Electro-oculograms. The formula used was,

$$EEG_c(i) = EEG_m(i) - (\theta_1 HL(i)HR(i) + \theta_2 VR(i) + \theta_3 HL(i) + \theta_4 HR(i)) \quad \text{for } 1 \leq i \leq N \qquad ...(5)$$

where $EEG_c(i)$ = i^{th} sample value of corrected EEG,
$EEG_m(i)$ = i^{th} sample value of measured EEG,
$HL(i)$ = i^{th} sample value of horizontal left EOG,
$HR(i)$ = i^{th} sample value of horizontal right EOG,
$VR(i)$ = i^{th} sample value of vertical right EOG,
N = number of data points,
and θ = transmission coefficient.

The values of θ were computed by a correlation technique (Jervis, et al., 1989b) using a non-recursive algorithm.

The preprocessed, averaged CNV waveforms of a normal subject, an HD patient, a schizophrenic patient, and a PD patient are shown in Figures 3a, 3b, 3c and 3d respectively. These examples were selected at random. It should be noted that large variations in the waveforms are found within patient categories and within normal subjects, and therefore it is

difficult to define a typical patient waveform.

4 Generation of the Discriminatory Variables

The CNV trials were preprocessed as described. Two segments from each CNV trial were selected. These were: a 512ms segment prior to the warning stimulus (pre-stimulus segment) and another 512ms segment prior to the imperative stimulus (post-stimulus segment). Each segment corresponded to 64 sample values. The next step was to transform the data sequences into the frequency domain using the discrete Fourier Transform (DFT). But prior to this transformation, the data was windowed and then augmented with zeros. The windowing was necessary in order to reduce the spectral leakage. Spectral leakage develops because the energy in the original spectral components leaks to the other frequency components after truncation in the time domain (Stark and Tuteur, 1979). This can distort the frequency spectrum by introducing spurious peaks or cancelling out true ones. To reduce this effect, the segments were subjected to a Kaiser-Bessel window (Harris, 1978). The Kaiser-Bessel window had been identified earlier as suitable for this application (Jervis et al., 1989a). The trade-off between the side-lobes level and main-lobe width for the spectrum is determined by a parameter, α. Experiments indicated that α=0.75 would produce a satisfactory compromise. Since the DFT of digital data is also discrete, any signal component which occurs at a frequency between the harmonics will have its energy shared between these harmonics and thus will distort them. In order to reduce this problem, the DFT harmonic separation had to be reduced by using augmenting zeros before transforming the data. After the zero augmentation, each segment contained 64 sample values and 960 zeros. Four statistical tests were applied to the first 96 harmonic frequency components of the spectrum. These tests which are valid

for the sample sizes involved were designed originally to investigate the composition of AEPs (Jervis et al., 1983). As the description of the tests is included in Jervis et al. (1983), only a very brief description of them follows.

4.1 Nearest and Furthest Mean Amplitude Test

This test was designed for analysing the variation of amplitudes with phase angles in the post-stimulus spectrum.

4.2 Pre- and Post-Stimulus Mean Amplitude Difference Test

The purpose of this test was to establish whether there was a significant difference between the amplitudes of the pre- and post-stimulus harmonics.

4.3 Rayleigh Test of Circular Variance

The Rayleigh test of circular variance (Mardia, 1972) was applied to the phase angles of each post-stimulus spectrum in order to determine whether the phase angles were distributed in a non-uniform manner.

4.4 Modified Rayleigh Test of Circular Variance

The difference between this test and the Rayleigh test of circular variance was that it considered both the amplitudes and the phase angles of each post-stimulus spectrum.

5 Variable Reduction

The application of the four statistical tests to the 96 frequency harmonics produced 384 variables. In order to select the most

discriminatory variables and to reduce their number, a series of tests were carried out by using the Statistical Analysis System (SAS) (1982) computer programs. The tests were: univariate test, t-test, and stepwise discriminant analysis (SDA). Again, all these tests were valid for the sample sizes involved.

The univariate test computed a test statistic for the null hypothesis that the input variables were a random sample from the normal distribution. It calculated the Shapiro-Wilk statistic, W (Shapiro and Wilk, 1965). Small values of W led to the rejection of the null hypothesis. The t-test was applied to the variables not rejected by the univariate test. The test computed the t- statistic based on the assumption that the variances of the variables from the two groups (ie. patient category and normal control, or patients of one category against patients of another category) are equal, and also computed an approximate t based on the assumption that the variances are unequal. The variables which showed significant difference between the two groups (at 10% significance level) were selected. The variables selected at this stage were then used in a SDA. The SDA was carried out by the SAS procedure, Stepdisc. The Stepdisc procedure selected a subset of the variables in order to produce a good discrimination model using stepwise selection. The variables selected by the Stepdisc procedure are shown in Table 2.

6 Classification Method

The classification of the individuals was carried out by using discriminant analysis (DA) (Morrison, 1976). The DA was implemented through the SAS procedure, Discrim. The Discrim procedure calculated the values which showed the probability of belonging to one or other group. Initially the patients of each category were matched with their age/sex

matched normal control subjects and their variables were analysed by the Discrim procedure. Then the patients with HD were age/sex matched (as closely as it was possible for us) with schizophrenic patients and their CNV variables were analysed by the Discrim procedure. This was repeated for HD and PD patients, and PD and schizophrenic patients. In order to make the best use of the recorded data, it was decided to use a leave-one-out approach. In this method, the variables of all the individuals, but one, in a patient category and their age/sex matched normal control subjects (or another patient category) were used in the Discrim procedure. The Discrim procedure used this data to generate a classification rule. Then this classification rule together with the variables of the subject not included in obtaining the classification rule were used by the Discrim procedure. This generated a probability which indicated to which category the subject belonged. This was carried out for all the individuals in the categories considered.

7 Results and Discussion

It was possible to differentiate between the HD, PD and schizophrenic patients and normal control subjects using the described technique (refer to Tables 3a-3c). It was also found that the method can be effective in differentiating between schizophrenic, PD and HD patients (refer to Tables 3d-3f). The following should be noted when considering the results shown in Tables 3a-3f.

(i) The study was based on a limited number of individuals, ie. 11 HD, 16 PD, 20 schizophrenic patients and 43 normal control subjects. Therefore it will be necessary to test the method on a larger number of individuals in order to establish whether it can be used as a routine clinical test for

differentiating these disorders.

(ii) The leave-one-out method of analysis ensured that the subjects included during the calibration of the discriminant analysis were excluded during the test phase and therefore the available data were effectively analysed.

(iii) Some of the patients included in this study were on medication related to their disorders. Therefore it will be necessary to carry out an analysis of the effects of medication on the patient identification results. This necessitates the recording of data from a larger number of patients and normal subjects. This could not be achieved in this study.

(iv) It was not possible for us to closely age match the patients when attempting to differentiate between the individuals from two patient categories. A reason for this was that the usual ages of onset of schizophrenia, PD and HD were not the same. Thus most of the schizophrenic patients were younger than the PD and HD patients.

(v) Severity of illness in the patients was discussed in section 2. Each patient category included some individuals with mild forms and some individuals with severe forms of their disorders. The method distinguished correctly all the HD patients. When differentiating between PD patients and normal control subjects, one PD patient (classed as grade 4) was misclassified. When differentiating between schizophrenic patients and normal control subjects, one schizophrenic patient (sum of scores=8) was misclassified. It was not possible to accurately differentiate between the mild forms and severe forms of each disease using the described technique.

The method could also as a whole or in parts be applied to other ERPs and it might be valuable in the differentiation of other patient categories

(such as manic depression).

8 Conclusion

The results obtained indicated that the technique of using signal processing and discriminant analysis applied to the CNV waveforms is valuable for differentiating between schizophrenic, Parkinson's disease (PD), and Huntington's disease (HD) patients and normal subjects. It was also useful in differentiating between HD and PD patients, PD and schizophrenic patients, and schizophrenic and HD patients. The method was aimed at assisting diagnosis and the avoidance of false diagnosis. The method might also prove applicable to other waveforms or disorders. This study was based on a limited number of patients and normal subjects and due to various constraints the test-retest reliability and the effects of medication on the test results were not be carried out.

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grades	number of patients	
	HD Patients	PD Patients
1	2	1
2	1	2
3	0	1
4	5	12
5	3	0

Table 1

categories	discriminatory variables
Huntington's disease patients vs. normal control subjects	$H_{14}T_3$, $H_{26}T_2$, $H_{71}T_1$
schizophrenic patients vs. normal control subjects	H_3T_3, H_5T_3, $H_{58}T_1$, $H_{72}T_4$ $H_{85}T_3$, $H_{88}T_1$
Parkinson's disease patients vs. normal control subjects	H_6T_1, $H_{18}T_3$, $H_{26}T_1$, $H_{37}T_4$ $H_{63}T_3$, $H_{86}T_1$, $H_{91}T_4$
Huntington's disease patients vs. schizophrenics	$H_{24}T_2$, $H_{28}T_2$, $H_{67}T_3$, $H_{72}T_1$ $H_{76}T_1$
Huntington's disease vs. Parkinson's disease patients	$H_{20}T_2$, $H_{38}T_1$, $H_{83}T_3$, $H_{93}T_2$
schizophrenics vs. Parkinson's disease patients	$H_{13}T_2$, $H_{26}T_2$, $H_{38}T_1$, $H_{72}T_1$

Table 2

parameters		subjects' categories	
		Huntington's disease	control subjects
numbers of subjects	total	11 (6 male)	11 (6 male)
	on drug	5	0
age	mean	53.73	50.09
	STD	10.97	10.53
	range	39 to 77	40 to 73
differentiation success rate in the test domain		100%	100%

Table 3a

parameters		subjects' categories	
		schizophrenic patients	control subjects
numbers of subjects	total	20 (15 male)	20 (15 male)
	on drug	18	0
age	mean	33.60	39.50
	STD	12.22	13.66
	range	20 to 68	22 to 75
differentiation success rate in the test domain		95.0%	100%

Table 3b

parameters		subjects' categories	
		Parkinson's disease	control subjects
numbers of subjects	total	16 (10 male)	16 (10 male)
	on drug	12	0
age	mean	63.63	50.81
	STD	9.68	11.16
	range	42 to 80	35 to 75
differentiation success rate in the test domain		93.8%	87.5%

Table 3c

parameters		subjects' categories	
		Huntington's disease	schizophrenic patients
numbers of subjects	total	11 (6 male)	11 (7 male)
	on drug	5	9
age	mean	53.73	40.64
	STD	10.93	12.34
	range	39 to 77	27 to 68
differentiation success rate in the test domain		100%	90.91%

Table 3d

parameters		subjects' categories	
		Huntington's disease	Parkinson's disease
numbers of subjects	total	11 (6 male)	11 (6 male)
	on drug	5	9
age	mean	53.73	60.91
	STD	10.97	10.52
	range	39 to 77	42 to 80
differentiation success rate in the test domain		90.91%	81.82%

Table 3e

parameters		subjects' categories	
		schizophrenic patients	Parkinson's disease
numbers of subjects	total	16 (12 male)	16 (10 male)
	on drug	14	12
age	mean	36.63%	63.63%
	STD	11.83	9.68
	range	25 to 68	42 to 80
differentiation success rate in the test domain		81.25%	93.75%

Table 3f

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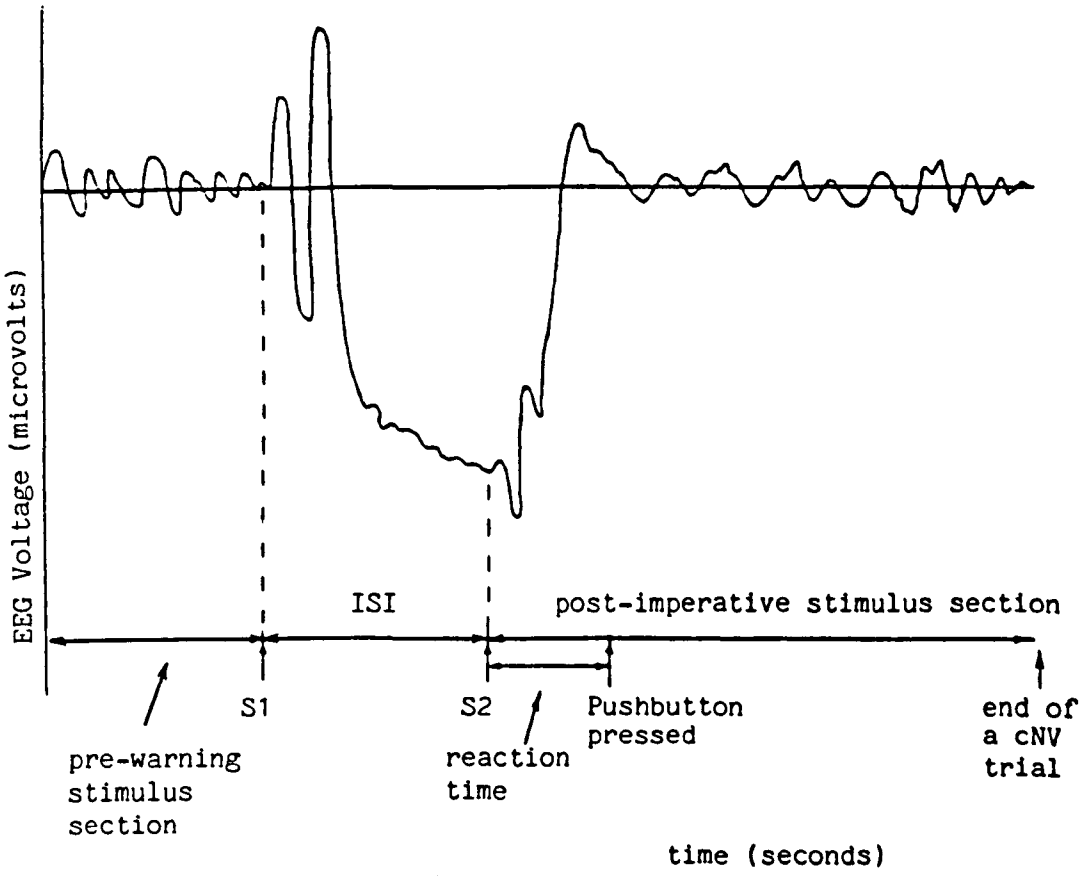

Figure 1 A Schematic drawing of a preprocessed averaged CNV waveform.

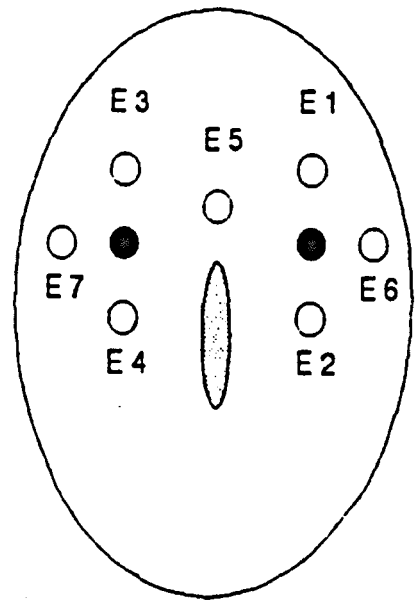

Figure 2 The positions of EOG electodes.

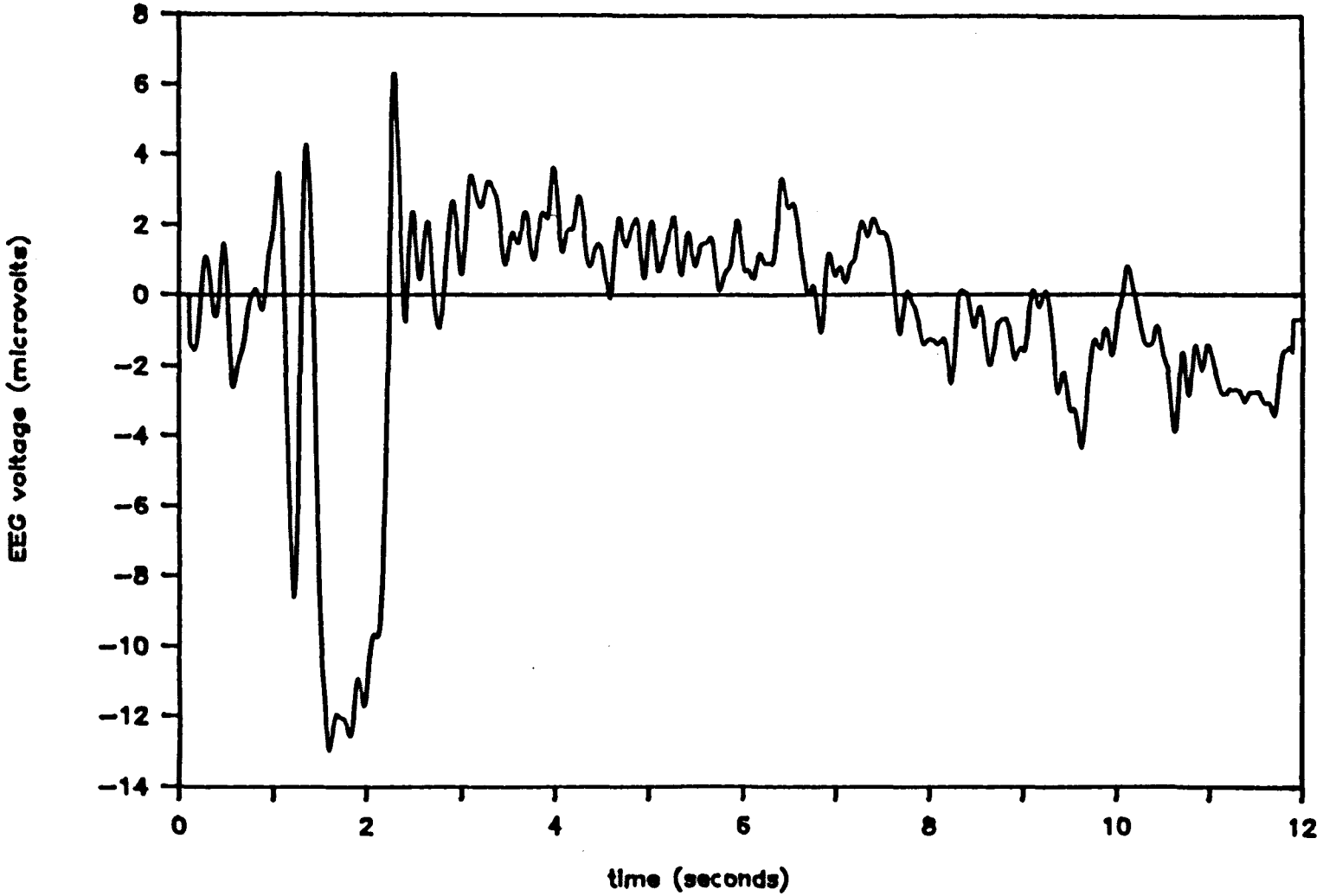

Figure 3a. The preprocessed averaged CNV response in a normal subject.

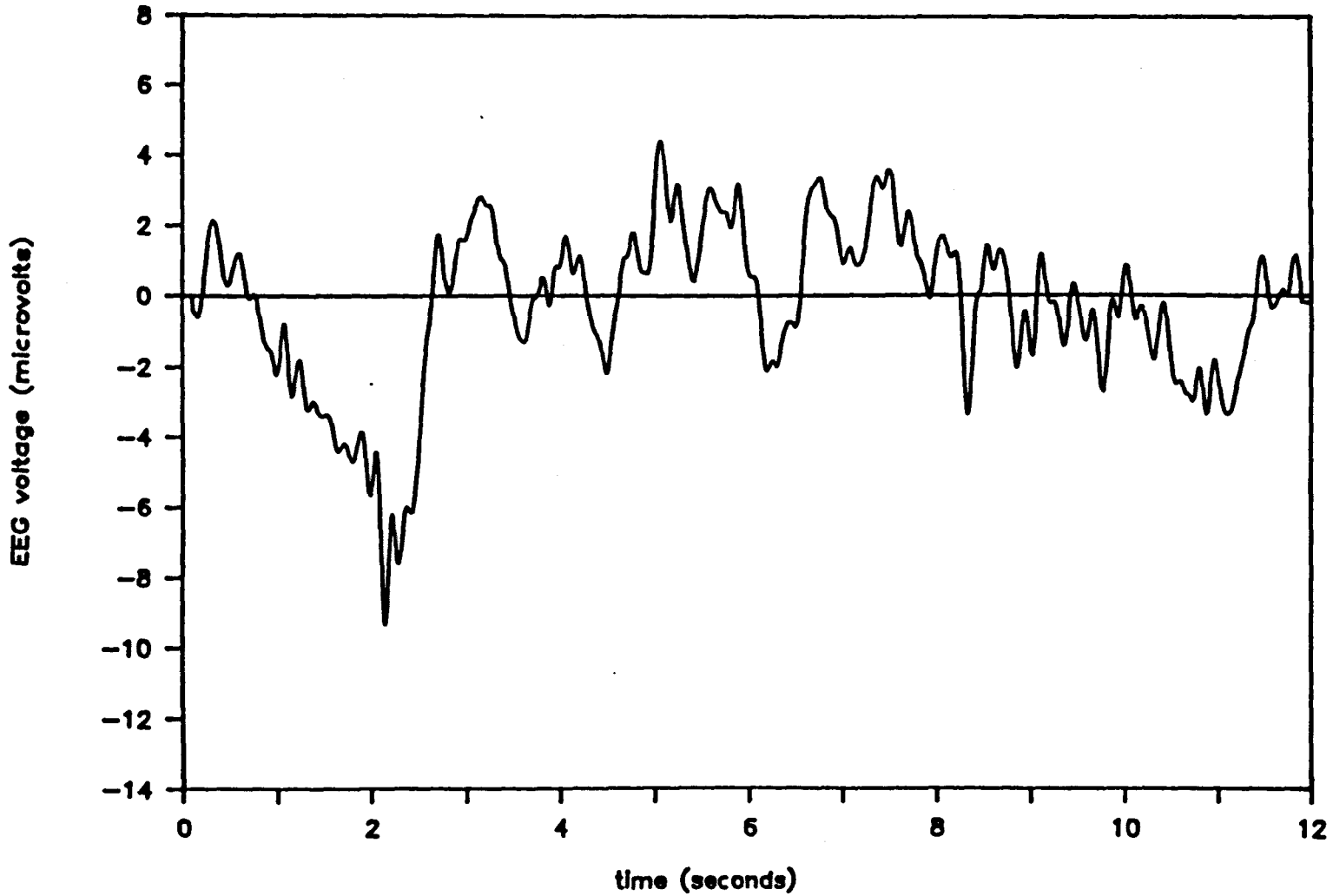

Figure 3b The preprocessed averaged CNV response in a Huntingon's disease patient.

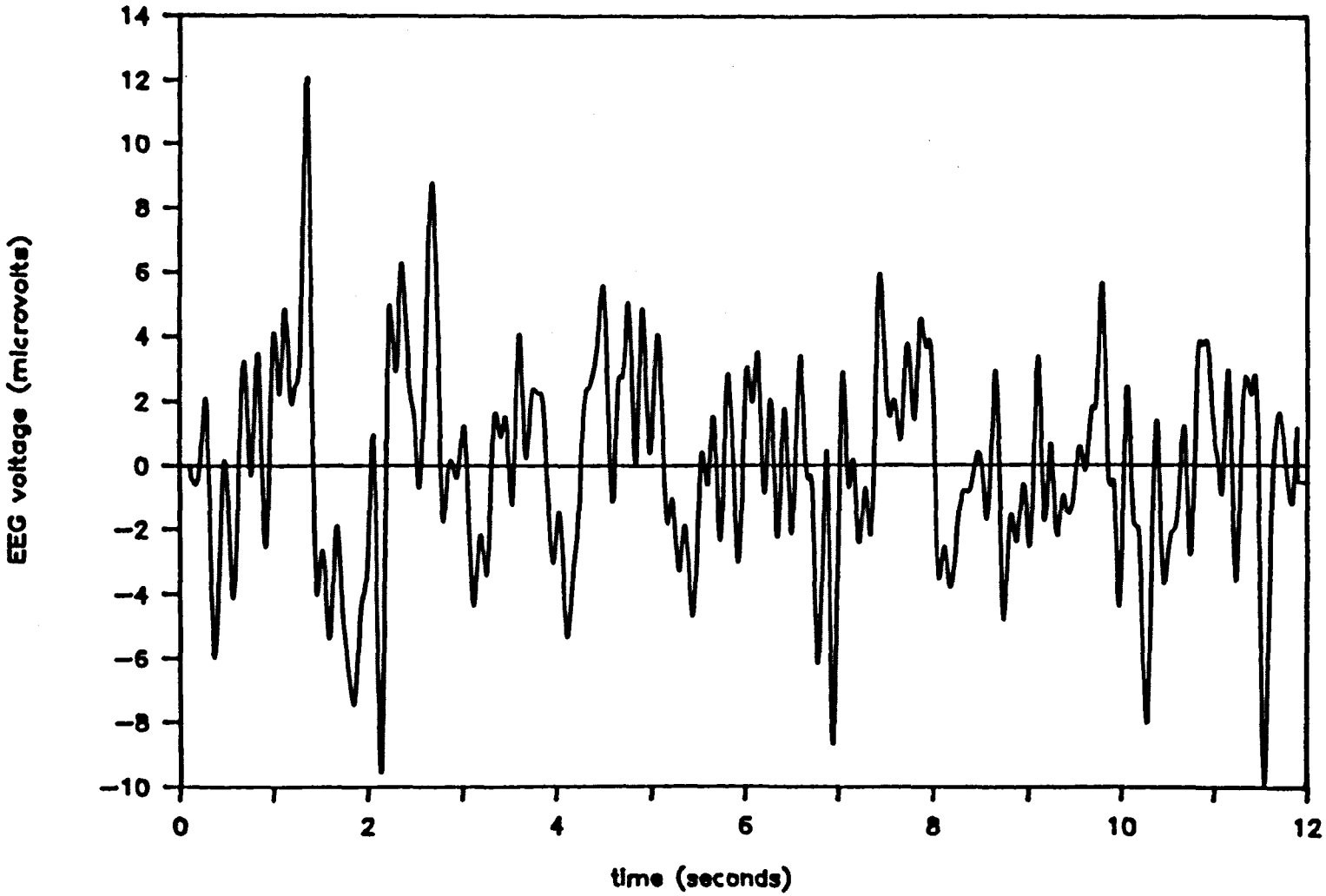

Figure 3c The preprocessed averaged CNV response in a Schizophrenic patient.

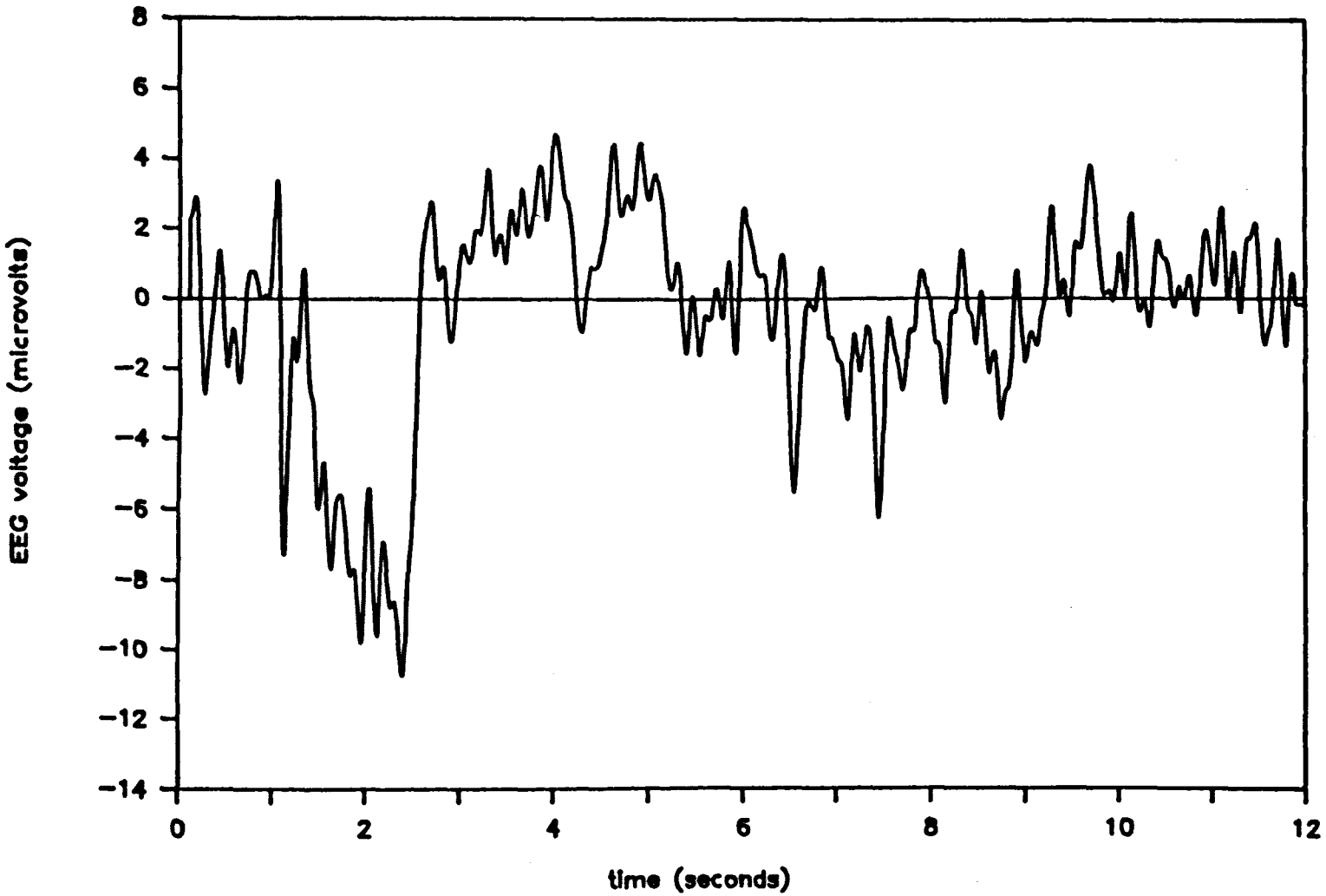

Figure 3d . The preprocessed averaged CNV response in a Parkinson's disease patient.